ANNALS OF SURGERY

VOL. 118 SEPTEMBER, 1943 No. 3

REGIONAL ILEITIS

JOHN W. HOLLOWAY, M.D.

CLEVELAND, OHIO

FROM THE DEPARTMENT OF SURGERY OF UNIVERSITY HOSPITALS OF CLEVELAND, AND THE WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE, CLEVELAND, OHIO.

IT IS THE PURPOSE OF THIS PAPER to report a series of cases of regional ileitis which, while not large, has been of such variation that it suggested the desirability of selecting those cases which might be utilized to outline a possible sequence of events from the standpoint of gross pathology. Many of the observations are largely confirmatory of the information already available in the voluminous literature on this subject. However, additional emphasis has been placed upon those aspects which appear to warrant it.

In their original article (1932) Crohn, and his associates[3], reported a series of chronic inflammatory lesions which consistently involved the terminal ileum, stopping abruptly at the ileocecal valve; their observations suggested that they were dealing with a definite clinical entity. Since that time contrary-minded individuals have reported somewhat similar lesions at higher levels in the small intestine, together with occasional manifestations in the large bowel. In all our cases, with the exception of Case 5, the localization has been as Crohn originally described it. He suggested that the ileocecal valve appears to function as a barrier to extension into the cecum. While reported cases may tend to refute this, several of ours were of some interest in this connection. We were privileged to carry out exploratory operations and resection in two cases (Cases 3 and 7) in which observations at operation six and eight years previously had indicated that the process stopped abruptly at the ileocecal valve. Examination of the resected specimen and examination at operation showed no further progression of the process into the cecum. However, in Case 3 the ileocolostomy might have been a limiting factor. In any event, about 80 to 90 per cent of the lesions reported have been limited to the terminal ileum.

From the clinical standpoint, Crohn, and his associates, divided the condition into four phases: First, the earliest manifestations of abdominal discomfort which may be vague or indefinite but in other instances may very closely simulate acute appendicitis. Second, the ulcerative stage, which is characterized by varying degrees of abdominal cramps and diarrhea accompanied on occasions by some anemia and loss of weight. Third, the fibrosing or stenotic phase which is typified by cramps which may be obstructive in

origin, together with intermittent episodes of diarrhea. On many occasions a mass is palpable in the right lower quadrant, and the patient may have a considerable degree of anemia and emaciation. Fourth, the phase characterized by fistula formation, which fistula may be internal or external. The former may be established between loops of small or large bowel, particularly the sigmoid (our experience is outlined in Figure 5). External fistulae may appear in the abdominal wall or perineum.

In attempting to coordinate the preceding with a subsequent classification, the first two phases probably represent acute and subacute manifestations, while the last two are definitely chronic; however, as mentioned elsewhere in this paper, the subacute stage may be the phase of actual perforation and beginning fistula formation. It should be emphasized that the progression may extend over years, and that on occasions there may seem to be a marked disparity between the severity of the symptoms and the extensive changes revealed by operation. Furthermore, in isolated instances the stenotic phase may manifest itself without any satisfactory history suggestive of progression through the early phases.

In an effort to establish the sequence of progression, we have selected Cases 1, 2, 5 and 9 because of the distinctive gross appearance of the lesions as revealed by operation. Case 1 (Fig. 1), because of the marked edema and abscence of accompanying local signs of inflammation, was thought to represent the earliest manifestations and is largely a question of lymphatic block. Case 2 (Fig. 2) would seem to be quite comparable with Case 1, there being, however, further superimposed signs of local inflammation, but still characterized by lymphatic block. Case 5 (Fig. 3), while the most striking, is surrounded with uncertainties from the standpoint of classification. Although in this case there was involvement of the terminal ileum, there was in addition segmental involvement; one area involved was the third part of the duodenum. Involvement of the duodenum grossly appeared comparable with the findings in Case 1, *i.e.*, marked edema with a paucity of inflammatory findings. It is reasonable to assume that the segmental areas had a similar origin though varying markedly in gross appearance. Whether we are entirely justified in classifying this manifestation with regional ileitis may be open to question. Except for the duodenal involvement, grossly, this case is identical with several cases described by Jackman[8] under the caption of "localized hypertrophic enteritis." The gross description and illustrations have much in common, and our information concerning the microscopic picture is drawn from this report. In any event, from the standpoint of history and microscopic findings we can definitely place it between Cases 2 and 9. Case 9 (Fig. 4) is obviously of considerable chronicity and typical of the obstructive and stenotic phase.

In using the terms "acute," "subacute" and "chronic," we are employing them in a strictly clinical sense, without implications as to the microscopic findings. This would seem particularly desirable because in some instances the chronic lesions may show superimposed acute inflammation, while the

so-called subacute case probably shows the most active inflammatory lesion microscopically.

If it is assumed that there is justification for utilizing the terms "acute," "subacute" and "chronic," it would seem desirable to review the available data in regard to the gross and microscopic pathology of regional ileitis. Grossly, the acute forms are characterized by their sharp demarcation, their sponge-rubber-like consistency, the marked edema which varies from white to pink, and the enlargement of mesenteric nodes of the involved segment. There is usually an accompanying accumulation of intra-abdominal fluid in the acute form. Grossly, the so-called subacute type is characterized by spongy consistency, sharp demarcation, and desquamation of the mucosa—in some instances in its entirety. The mucosa has been replaced by an hemorrhagic exudate, which, together with engorgement, is visible through the more or less normal peritoneum and which accounts for the fiery red appearance of the lesion grossly. Its appearance at operation may suggest recent strangulation or some embolic phenomenon. The bowel may be friable, and the two specimens of the subacute type reported in the literature (Jackman) were obtained incidental to perforation through handling. Hence, in all likelihood perforation and fistula formation may frequently occur spontaneously during this phase. After having passed through this reaction, it would seem that an intestine so affected must necessarily continue ultimately to the stenotic or fistula stages, there being little possibility of spontaneous subsidence. Grossly, the chronic forms are characterized by their thickening, rigidity and tumor formation either because of their altered character or because of adhesions between adjoining loops or extensive inflammatory reaction in lymph nodes or the adjacent mesentery. The mucosa is extensively involved by ulceration, varying in depth, but largely distributed along the mesenteric border of the intestine, with areas in which the lumen is markedly diminished in caliber. There is little or no accumulation of intra-abdominal fluid in the chronic form.

From the microscopic standpoint, there is nothing which is characteristic of this lesion. In view of the fact that practically all specimens obtained are of the chronic or subacute types, we have less conception of the microscopic appearance of the acute forms, particularly the edematous type. However, one might assume that, microscopically, the acute forms might reveal slight ulceration of the mucosa with marked thickening of all layers of bowel due to associated edema and with an infiltration of cellular elements dependent upon the severity of the reaction. Histologically (Jackman), the subacute condition is characterized by the absence of mucosa with substituted hemorrhagic exudate and an underlying submucosal reaction which almost borders on abscess formation. The peritoneum is relatively uninvolved, but intermediary layers reveal some degree of fibrosis indicative of previous inflammation. However, there is no demonstrable evidence of thrombosis, which is of interest in view of its gross appearance. Histologically, the chronic forms reveal ulceration of the mucosa of varying extent and depth with thickening

of walls and stenosis due to fibrosis, and with an infiltration of inflammatory cells which may vary depending upon the severity of the reaction. Giant cells may be present.

From the standpoint of etiology, rather exhaustive attempts have been made to determine some specificity, but to date there is nothing that has proved convincing. Tuberculosis has been fairly well excluded. Experimentally, Reichert and Mathes[16] are said to have injected the corresponding lymphatics with a sclerosing agent and thus produced a lesion in the bowel which simulated the acute edematous lesion. In connection with the established observation that the process frequently stops abruptly at the ileocecal junction, one may refer to recent studies of the ileocecal region by Bargen, Wesson and Jackman.[1] They concluded that, mechanically, the ileocecal region functioned as a valve and that there was a marked diminution or actual interruption of the communications of the submucosal lymphatics in the region of the labia of the valve. Since, at least in the acute phase, its most striking and most obvious manifestation is in the form of lymphatic block, the preceding may explain the tendency for localization proximally.

The question of differential diagnosis in the acute phase is extremely difficult, and if exploration is carried out it is usually undertaken with a diagnosis of acute appendicitis. At the moment, we are referring to those instances in which the first symptoms have not extended back more than 36 or 72 hours. In our experience, it may present any of the variations of symptoms associated with acute appendicitis. Thus far, we have found no differential point which would justify a clinical distinction, although in some instances there is a history of a slight change in bowel habits for three to six months before the attack. On occasions, there has been more in the way of cramps than we usually associate with appendicitis; vomiting infrequent. However, we wish to emphasize that from a practical standpoint the differential diagnosis probably cannot and should not be attempted. While we are not certain, we are inclined to believe that roentgenologic studies would be of little value in the acute stages and, in general, would be contraindicated.

In our experience, roentgenologic studies in the acute cases, six to eight weeks following the establishment of the diagnosis by operation, have failed to reveal any findings that were diagnostic. To be sure, in most instances there had been a complete subsidence of symptoms postoperatively. However, this may either indicate inadequacy of roentgenologic diagnosis in the acute phase or the absence of roentgenographic findings may accompany subsidence of the lesion. The latter possibility certainly supports conservative therapy in the acute phases when encountered at operation.

In the instance referred to as subacute, roentgenography might show narrowing; however, in view of the associated friability this might well be undesirable. Otherwise, our single case was characterized by cramps, an elevated white blood cell count, and the passage of several grossly bloody stools.

The chronic forms present much less of a problem from the diagnostic standpoint, but do require distinction from malignant growths and specific

granulomata. However, for practical reasons surgical intervention would probably prove to be the method of choice in any event. Roentgenologic studies in this type can be extremely helpful, and the so-called "string sign" in many instances is almost diagnostic. Chronic ulcerative colitis may simulate regional ileitis, although the localization roentgenologically of the lesion in the colon and the presence of mucosal ulceration as revealed by sigmoidoscopic examination aid materially in making the distinction. It is of further interest that in many instances the palpable mass, at least clinically, suggested a pelvic lesion; however, roentgenograms of the gastro-intestinal tract aided in making the distinction.

There is some difference of opinion in regard to the course to follow when the acute case is encountered at operation. There is little support for immediate radical resection. It is our definite impression that some of these subside completely, or at least remain subclinical, during the period of observation. In the series of six cases of Koster, Kasman and Sheinfeld,[19] subsequent intervention was not required during the period of observation, and this coincides with our own experience. More recently, Smithy[18] has reported a series of acute cases of regional ileitis which lends additional support to conservative therapy in such instances. However, others have reported a very high percentage of ultimate interventions in acute cases. When the cecum is uninvolved (100 per cent in our series), we have routinely carried out appendicectomy, not with the idea that appendicectomy contributed therapeutically, but because it is reassuring to have removed the appendix should there be a chronic complaint in the right lower quadrant. If a radical procedure seems indicated subsequently, it can frequently be carried out more advantageously at a second operation.

Mixter[12, 13] has condemned the practice of appendicectomy in the acute cases because of the danger of fistula formation. However, in the early manifestations, in the presence of an uninvolved cecum, there should be little danger of fistula formation as a result of the appendicectomy. In any event, as Crohn, and his associates, have indicated, the fistulae frequently have their origin from the ileum rather than from the appendiceal stump. Hence, they may develop incidental to the exploration rather than as a result of the appendicectomy.

Insofar as the chronic stenosing types are concerned, there is general agreement that short-circuiting anastomotic procedures or resection should be carried out, with the latter procedure in considerable favor, although Ginzburg and Garlock[5] have recently presented excellent evidence in favor of ileocolostomy, with exclusion. In the majority of instances great benefit follows the aforementioned procedures, although it is not uncommon for those patients who secure a satisfactory result to have two to three soft stools a day. Recurrences of symptoms are quoted in the neighborhood of 10 to 15 per cent, while Cutler[4] mentions a much higher figure, and is pessimistic as to the benefits of surgical intervention. However, in view of the occasional segmental involvement recurrences might well be anticipated.

Our experience with the chronic stenotic phases has been limited to seven cases, all except one of which have been treated by primary resection of the terminal ileum and cecum, with lateral anastomosis between the ileum and ascending colon. In a single instance an ileocolostomy had been carried out elsewhere two years previously, and we performed resection of the isolated loop. The foregoing procedures have been effected without mortality, and in five of the seven cases the results are quite satisfactory to date. Of the unsatisfactory, one was considered quite satisfactory for a period of four years, after which time a severe macrocytic anemia and a marked rectal stricture, of undetermined origin, developed. The remaining patient (with initial ileocolostomy), although maintaining her nutrition, continued to complain of cramps and diarrhea, and was considered to have an unsatisfactory result.

We have attempted to arrange the more characteristic examples of our cases in the sequence in which we believe the condition progresses, recognizing the hazard of doing so with a no more reliable basis than their gross appearance. We have further classified them as acute, subacute and chronic. It would seem that there is adequate support for conservative therapy in the acute manifestation. The subacute stage, because of its friability and tendency to perforation, might well require resection. We believe the chronic stenotic phase to be definitely amenable to surgical treatment, with primary resection as the procedure of election in our cases.

CASE REPORTS

Case 1.—J. L., white, male, age 21, was admitted to Lakeside Hospital, April 14, 1933, with a history of abdominal cramps of three to four days' duration; the pain had ultimately tended to localize in the right lower quadrant. There had been several liquid stools at the onset but subsequently the bowel movements were normal. There had been no vomiting. There was no history of previous similar difficulty. The patient was very muscular and well nourished. There was some tenderness in the right lower quadrant with marked rebound tenderness, but little, if any, spasm. Rectal examination was essentially negative. Temperature 38.5° C., pulse 90; white blood cell count 7,000; uranalysis negative.

The patient was observed for six hours, after which time an exploratory operation was carried out, through a McBurney incision. Some fluid was encountered. The terminal 12 to 14 inches of ileum was found to be markedly thickened and edematous; it was a white edema, and there was no injection (Fig. 1). The nodes of the involved segment were enlarged. The process stopped abruptly at the ileocecal valve. The cecum and appendix were not involved. No other abnormalities were noted. Appendicectomy was performed. The wound was closed without drainage. No pathologic diagnosis was made. Convalescence was uneventful. Stool cultures and agglutination tests were negative for *B. typhosus para* A and B. During the subsequent year the patient had no further trouble; after that we were unable to follow him. *Diagnosis:* Regional ileitis (acute).

Case 2.—H. K., white, female, age 31, began experiencing generalized abdominal cramps about 24 hours before admission to Lakeside Hospital, April 30, 1937. The discomfort subsequently localized in the right lower quadrant. There was some nausea but no vomiting or diarrhea. She had had some slight abdominal discomfort two weeks previously, but otherwise no similar previous difficulty, although for the preceding six months she had had several soft movements daily, when previously there

FIG. 1.—Case 1: Color drawing of operative findings: Primarily lymphatic block, characterized by edema, and peritoneal fluid, but with no other signs of inflammation. Classified as acute regional ileitis upon basis of history and findings.

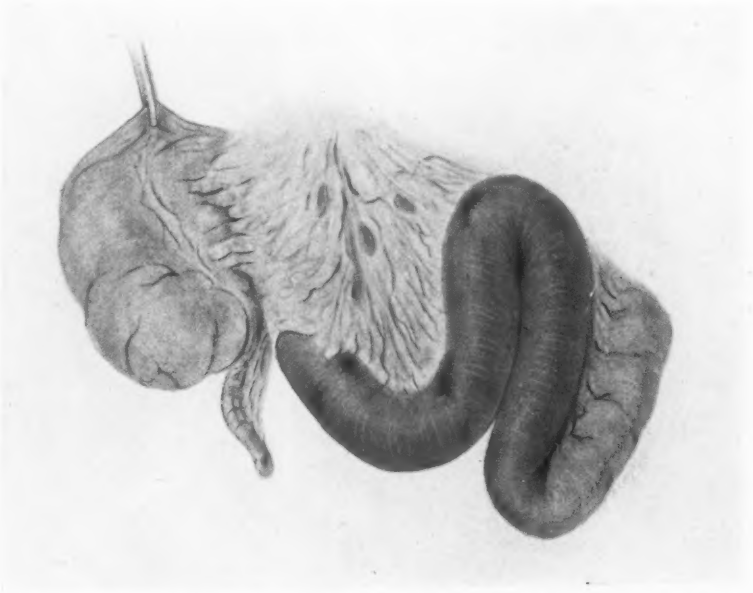


FIG. 2.—Case 2: Color drawing of operative findings: Lymphatic block not so obvious but inflammatory reaction extreme. Little fluid, but segmental, inflammatory involvement of ileum striking, suggesting recent embolic phenomena or strangulation; contrasted with edematous manifestations in duodenum comparable to Figure 1. Classified as subacute and acute regional ileitis upon basis of history and associated duodenal manifestation of an obviously acute nature. Only case in series with grossly bloody stools, although there is a history of gross hemorrhage in Case 7.

FIG. 3.—Case 5: Color drawing of operative findings: Lymphatic block with superimposed signs of moderate inflammation, characterized by edema, peritoneal fluid, and redness. Classified as acute regional ileitis upon basis of history and additional signs of early inflammation.

FIG. 4.—Case 9: Color drawing of resected specimen: Little evidence of lymphatic block; lesion of obvious chronicity, with fibrotic changes constituting a definite tumor.

had been but one. A questionable diagnosis of gastric ulcer had been made nine years before.

Examination revealed a well-nourished individual, not appearing acutely ill. There was definite tenderness in the right lower quadrant but no spasm. Rectal and vaginal examinations were essentially negative. Temperature 37° C.; white blood cell count 9,000 to 13,000; urine essentially negative. The patient was observed for four hours, and it was then deemed advisable to rule out appendicitis.

The patient was operated upon through a McBurney incision. A large amount of free fluid was encountered. The terminal ileum for a distance of 14 inches from the ileocecal valve was thickened, edematous and of a reddish-pink color (Fig. 2). The nodes in the corresponding segment of the mesentery were enlarged. The process stopped abruptly and did not extend beyond the ileocecal valve. The cecum and appendix were not involved. Appendicectomy was performed. No pathologic diagnosis was made.

The hospital course was uneventful. The patient had roentgenograms of the gastrointestinal tract, July 29, 1937, April 27, 1940 and September 9, 1941, with essentially identical findings, *viz.*, hypermotility and hyperperitalsis of small intestines, without deformity in terminal ileum or elsewhere. The patent's general health to date has been excellent, with no noteworthy abdominal symptoms. *Diagnosis:* Regional ileitis (acute).

Case 3.—L. W., white, female, age 26, was admitted to Lakeside Hospital, August 6, 1935, with the complaint of abdominal cramps and diarrhea. The patient apparently had been in good health until seven years before, at which time she began having cramps and diarrhea. Five years before admission she was admitted to another hospital, observed and operated upon for anal abscess and fissure. One year later she returned to the same institution and an abdominal exploration was carried out. A bilateral salpingectomy, left oophorectomy and appendicectomy were performed. Further exploration revealed a regional ileitis involving the terminal 18 inches and stopping abruptly at the ileocecal valve. A lateral anastomosis was performed about the lesion. The patient experienced marked benefit for a period of two years, when a recurrence of symptoms occurred which continued to time of admission to this hospital.

There had been some recent loss of weight and stools five to ten times a day, but no pus or blood were noted. The patient was well nourished. The general physical examination was negative save for some tenderness in the right lower quadrant. Laboratory data were negative except for hemoglobin of 60 per cent, and red blood cell count of 3,700,000. A barium enema revealed a functioning anastomosis, and findings in the terminal ileum suggestive of ileitis. In view of recurrence of symptoms, exploration was thought justifiable. Many adhesions were encountered, and a process was found in the terminal ileum characterized by thickening and edema, stopping abruptly at the ileocecal valve and extending up to about eight inches from the anastomosis. There was no fluid. Exploration of the remaining small and large intestine showed no involvement. Without disturbing the anastomosis, the short-circuited intestine (60 cm.) was resected to include a small portion of cecum. Grossly, the resected portion was comparable with findings in chronic regional ileitis, and the histologic examination was consistent with that diagnosis. The lesion did not extend beyond the ileocecal valve.

The postoperative course was uneventful. The patient was readmitted to the hospital one year later, with the history that, while there had been temporary benefit following operation, at the time of admission there was a recurrence of cramps and diarrhea. However, there had been no loss of weight and the previous moderate anemia had disappeared. *Diagnosis:* Regional ileitis (chronic). Result unsatisfactory. Recently readmitted for further resection.

Case 4.—J. W., white, male, age 30, was admitted to Lakeside Hospital, March 15, 1937, with a complaint of abdominal cramps and loose bowel movements of two

or three days' duration. Although discomfort was rather diffuse, there was a tendency to localization to the right of the umbilicus. There had been no nausea or vomiting. There was a history of episodes of diarrhea of very brief duration for several years, but at no time had there been cramps of the present severity.

The patient was a well-nourished, almost obese male. Examination of the abdomen revealed rather diffuse tenderness, most marked to the right of the umbilicus. There was no spasticity. There was definite rebound tenderness. Temperature 38° C., white blood cell count 16,000; urine essentially negative. The patient was observed for 12 hours, during which time discomfort increased and there was some further localization in the right lower quadrant. Prior to operation the temperature was 38.2° C.; white blood cell count 24,000.

Exploration was carried out through a McBurney incision, with a diagnosis of questionable acute appendicitis. Considerable fluid was encountered. The terminal ileum, for a distance of 16 inches, was quite red, thickened and edematous. The process terminated abruptly at each end and stopped abruptly at the ileocecal valve. There were enlarged nodes in the segment of mesentery of the involved bowel. The cecum and appendix were not involved. An appendicectomy was performed. No pathologic diagnosis was made.

The subsequent hospital course was uneventful. Roentgenograms of the gastrointestinal tract, September 8, 1937, revealed no abnormalities. The patient has had no further trouble to date. *Diagnosis:* Regional ileitis (acute).

Case 5.—F. S., white, male, aged 27, was admitted to Lakeside Hospital, April 2, 1934, with a history of having been in good health until five days before admission. At this time he experienced abdominal pain, more marked in the left lower quadrant than the right, and accompanied by nausea and vomiting. There had been obstipation but the patient had passed flatus. An appendicectomy had been performed through a right rectus incision four years before, and a few months thereafter a bilateral inguinal herniorrhaphy.

Examination showed a slightly undernourished and pallid appearing individual, not acutely ill. The abdomen was possibly slightly distended but there was no visible peristalsis. There was some tenderness in the left lower quadrant but no spasm. There were scars of a right rectus incision and of bilateral inguinal herniorrhaphy. Temperature 37.8° C.; white blood cell count 21,000; urine essentially negative. Our impression was partial intestinal obstruction. A barium enema revealed no abnormalities, and because of persistence of vomiting in the absence of distention, we suspected a high obstruction. A small amount of barium by mouth revealed partial obstruction in the region of the second and third part of the duodenum. The patient was observed for nine days, after which time he passed several grossly bloody stools.

Exploration was immediately carried out, with a diagnosis of partial intestinal obstruction. The right rectus scar was excised and the peritoneal cavity was entered. A small amount of slightly cloudy fluid was encountered. After freeing many adhesions, we encountered two striking areas of segmental involvement of ileum measuring 12 to 18 inches in extent, one of which extended up to, and stopped abruptly at the ileocecal valve (Fig. 3). The bowel over the involved area was a fiery red color with no extension of the process into the mesentery. There was some segmental thickening and enlargement of nodes in the mesentery. Our first impression was that it was some embolic phenomenon or a recently released volvulus, but the condition of the mesentery ruled this out. Exposure of the third part of the duodenum (indicated in the roentgenogram) revealed marked edema involving the peritoneum and that partion of the duodenum observed. It was a white edema and in marked contrast to the process at previously described levels. In view of the extent of the process, resection was not contemplated.

The postoperative course was quite uneventful save for a continuance of bloody diarrhea for several days and a moderate parotitis. The patient was followed for about two and one-half months after operation, during which time he gained considerable weight and was entirely free of the symptoms which brought him to the hospital. We were unable to follow him after this time. *Diagnosis:* Regional ileitis (subacute).

Case 6.—M. T., white, female, age 34, was first admitted to Lakeside Hospital, July 1, 1935, with a history of diarrhea (5 to 15 stools daily) and vague abdominal discomfort of some four years' duration. There had been an accompanying loss of weight. Following investigation, her condition was diagnosed as enterocolitis of undetermined origin, although in view of many sensitivities it was considered as possibly allergic in origin. The patient was apparently somewhat improved until six months before the present admission, at which time there was an exacerbation of symptoms, *i.e.*, diarrhea (4 to 8 stools daily) and cramps of increasing severity.

At the admission on September 13, 1937, the patient was moderately well-nourished, and did not appear acutely ill. The general physical examination was essentially negative save for lower abdominal tenderness in both quadrants, more marked on the right where there was a definite, tender palpable mass. Barium enema revealed a typical "string sign" of the terminal ileum. This was confirmed by roentgenograms of the gastro-intestinal tract. Hemoglobin 78 per cent; white blood cell count 8,000; red blood cell count 4,200,000; urinalysis essentially negative. Stools: No entemeba, benzidine 2–3 +++. In view of the progressive symptoms and obvious early obstruction, resection was deemed advisable.

At operation, the terminal two and one-half feet of ileum presented the typical picture of chronic ileitis, with the process stopping abruptly at the ileocecal valve. The cecum and appendix were not involved grossly. The involved portion of the ileum and part of the cecum were resected, and a lateral ileocolostomy was carried out. Microscopically, the lesion was consistent with the usual picture of chronic regional ileitis. The process stopped at the ileocecal valve, although there was some slight involvement of the cecum, but merely what one might anticipate of tissues in juxtaposition to such a process.

The postoperative course was uneventful. Following discharge from the hospital the patient did exceedingly well, gained weight and was quite comfortable. She had two or three soft formed stools a day. *Diagnosis:* Regional ileitis (chronic).

About July 17, 1941, the patient complained of dizziness, weakness, shortness of breath and pain upon defecation. Investigation revealed an hemoglobin of 35 per cent; red blood cell count of 1,400,000; and white blood cell count of 3,350. Proctoscopic examination revealed a stricture about two inches from the anus. Biopsy of this was negative. Several Frei tests were inconclusive. *Diagnosis:* Macrocytic anemia due to deficient absorption; stricture of rectum of undetermined origin. Result unsatisfactory.

Case 7.—A. K., white, female, age 40, was admitted to Lakeside Hospital, July 20, 1936, with a history of abdominal discomfort for some ten years. At onset, ten years previously, an appendicectomy was carried out at another hospital, which procedure was followed by a fistula. Some time thereafter the fistulous tract was excised, and it was found to communicate with a lesion in the terminal ileum, which was described as typically tuberculous, although there was no histologic confirmation. Some type of resection was carried out. The patient did fairly well until three or four years before the admission to Lakeside Hospital, at which time she experienced abdominal cramps, diarrhea and loss of weight. Two years before admission she had had a severe hemorrhage. The aforementioned symptoms persisted, and the patient followed a downhill course until the admission to Lakeside Hospital.

The patient was quite emaciated and obviously chronically ill. General examination was negative save for abdominal findings. There was a small hernia in the supra-

pubic scar, but no mass was palpable. However, on pelvic examination there was a definite mass filling the pelvis which was difficult to separate from the uterus. Hemoglobin 35 per cent, red blood cell count 2,000,000; white blood cell count 4,000. Roentgenograms revealed deformity of the terminal ileum, and suggested that the mass in the pelvis represented the terminal ileum. Although the patient was a bad risk, exploration was thought advisable.

At operation, the mass in the pelvis was delivered readily and was found to consist of a mass of agglutinated small bowel, apparently centering about the terminal ileum. There was one loop of jejunum so intimately involved that resection and end-to-end anastomosis were carried out (Fig. 5A). Following this it was feasible to resect the terminal 45 cm. of ileum and the cecum, a lateral ileocolostomy being carried out.

The patient's course was stormy for several days after operation but uneventful thereafter. She was completely relieved of all symptoms, and gained 45 pounds in the first year. The patient continues to have two to three soft movements a day, but they are not accompanied by discomfort. She remains well to the present time. *Diagnosis:* Regional ileitis (chronic).

Case 8.—M. L. H., white, female, age six years, was admitted to Glenville Hospital in September, 1936, with a history of periumbilical and right lower quadrant cramps of 48 hours' duration. There was no history of any similar previous difficulty. Bowel movements had been regular.

Examination revealed a moderately well-nourished white female, who did not appear seriously ill. There was some tenderness in the right lower quadrant but neither rigidity nor distention. Temperature 38° C.; white blood cell count 11,000; urine negative. In view of the persisting cramps it was deemed advisable to carry out an exploratory operation, with a diagnosis of acute appendicitis or some type of partial obstruction.

Under gas-oxygen-ether anesthesia, a short right rectus incision was made. The peritoneal cavity contained considerable clear fluid, the appendix was normal. However, the terminal five inches of ileum was markedly edematous and of a pinkish color; nodes in the involved segment were definitely enlarged; the cecum was not involved. Appendicectomy was performed. No pathologic diagnosis was made.

The subsequent hospital course was uneventful. Insofar as can be ascertained the child has had no further trouble. *Diagnosis:* Regional ileitis (acute).

Case 9.—S. B., a white, female, age 20, was admitted to Lakeside Hospital, December 28, 1937. Four years previously she had been admitted to the hospital with a history of vague abdominal complaint of some four days' duration, localizing in the right lower quadrant, unaccompanied by nausea or vomiting. An appendicectomy was performed, without abdominal exploration. The histologic report was chronic appendicitis. Following this, the patient continued to have episodes of abdominal cramps accompanied by distention. In general, the discomfort increased in severity and was, on occasion, accompanied by fever and gradual loss of weight. More recently, there had been some relation to the menses, particularly the last, which began some ten days previously, and was accompanied by fever and the finding of a mass in the right lower quadrant, which was thought to have its origin in the pelvis.

The patient was operated upon on the Gynecological Service, with the diagnosis of possible ovarian cyst.

At operation, the mass was found to have its origin in the terminal 12 inches of the ileum, with extensive involvement of nodes in the corresponding segment of the mesentery. The lesion was obviously chronic and the site of fibrous changes (Fig. 4). There was no fluid. The ileum and a portion of the cecum were resected and a lateral ileocolostomy was carried out.

Histologic Report: Pathologic findings consistent with chronic regional ileitis.

The postoperative course was uneventful for the first week. On the tenth postoperative day the patient was operated upon again because of intestinal obstruction. An adhesion to the midline scar had produced complete obstruction of the small intestine at a level about four feet above the anastomosis. The subsequent course was uneventful. Since that time, the patient has gained considerable weight and, in general, is quite comfortable. She does have from one to three soft stools per day; when under nervous strain this may border upon diarrhea. *Diagnosis:* Regional ileitis (chronic).

Case 10.—W. H., white, male, age eight, was admitted to Lakeside Hospital, August 2, 1938. Three days before admission he began having abdominal discomfort, more marked on the right side than on the left. There had been no nausea, vomiting or diarrhea. There had been some abdominal discomfort one year previous to admission.

Examination revealed a moderately well-nourished boy, who did not appear acutely ill. There was some tenderness in the right lower quadrant but no spasm. Temperature 38° C.; white blood cell count 8,600; urine negative. The diagnosis was indefinite, but after 18 hours' observation there was no change in the findings and exploration was carried out through a McBurney incision. (The patient's family had had a recent unfortunate experience with peritonitis from a ruptured appendix).

At operation a moderate amount of fluid was encountered. The terminal three inches of ileum was thickened and edematous, but only slightly injected. A number of enlarged nodes were palpated in the mesentery. The process stopped abruptly at the ileocecal valve. The cecum and appendix were not involved. The latter was removed. There was no pathologic diagnosis.

The postoperative course was uneventful. The patient had roentgenograms of the gastro-intestinal tract, April 20, 1939, with no unusual findings. His general condition to date has been excellent, with no recurrence of symptoms. *Diagnosis:* Regional ileitis (acute).

Case 11.—L. D., white, female, age 30, was admitted to Lakeside Hospital, March 2, 1939. She had apparently been in excellent health until six months before admission, when she began experiencing vague abdominal discomfort characterized by a feeling of distention; there had been no diarrhea. For the preceding eight weeks there had been a continuance of the foregoing symptoms with the addition of night sweats and intermittent elevation of temperature. About ten days before admission there had been a severe episode of abdominal pain, which localized in the right lower quadrant, with accompanying nausea and vomiting. Upon admission to the hospital the patient appeared chronically ill.

General examination revealed no abnormalities. Examination of the abdomen revealed a firm, somewhat tender mass in the right lower quadrant, measuring 8 x 6 x 6 cm. It was slightly movable and could be readily palpated on vaginal examination. Temperature 39°C.; hemoglobin 80 per cent, red blood cell count 4,300,000; white blood cell count 23,000; urine essentially negative. In view of the history, an appendiceal abscess was considered, but the impression rather favored regional ileitis. The temperature subsided in two weeks and a barium enema revealed a "string sign." A diagnosis of chronic regional ileitis was made. The patient was readmitted several weeks later for operation. Signs of inflammation were entirely absent; otherwise the findings were the same.

At operation, an inflammatory mass was found in the right lower quadrant, consisting primarily of thickened and fibrosed terminal ileum but further contributed to by adhesion of an adjacent loop of small bowel, omentum and the transverse colon (Fig. 5 B). There was no fluid. The terminal ileum and a portion of the cecum were resected, and an ileocolostomy was carried out. Grossly, the cecum was not involved; however, the ileocecal valve projected into the cecum in a cervix-like fashion. Microscopically,

there were the usual findings in the ileum with only the degree of reaction in the cecum that would occur in any stricture in juxtaposition. The postoperative course was uneventful. There was some diarrhea for several weeks following discharge. At the present time the patient's condition is excellent. She has gained weight. She does have two or three soft movements per day. *Diagnosis:* Regional ileitis (chronic).

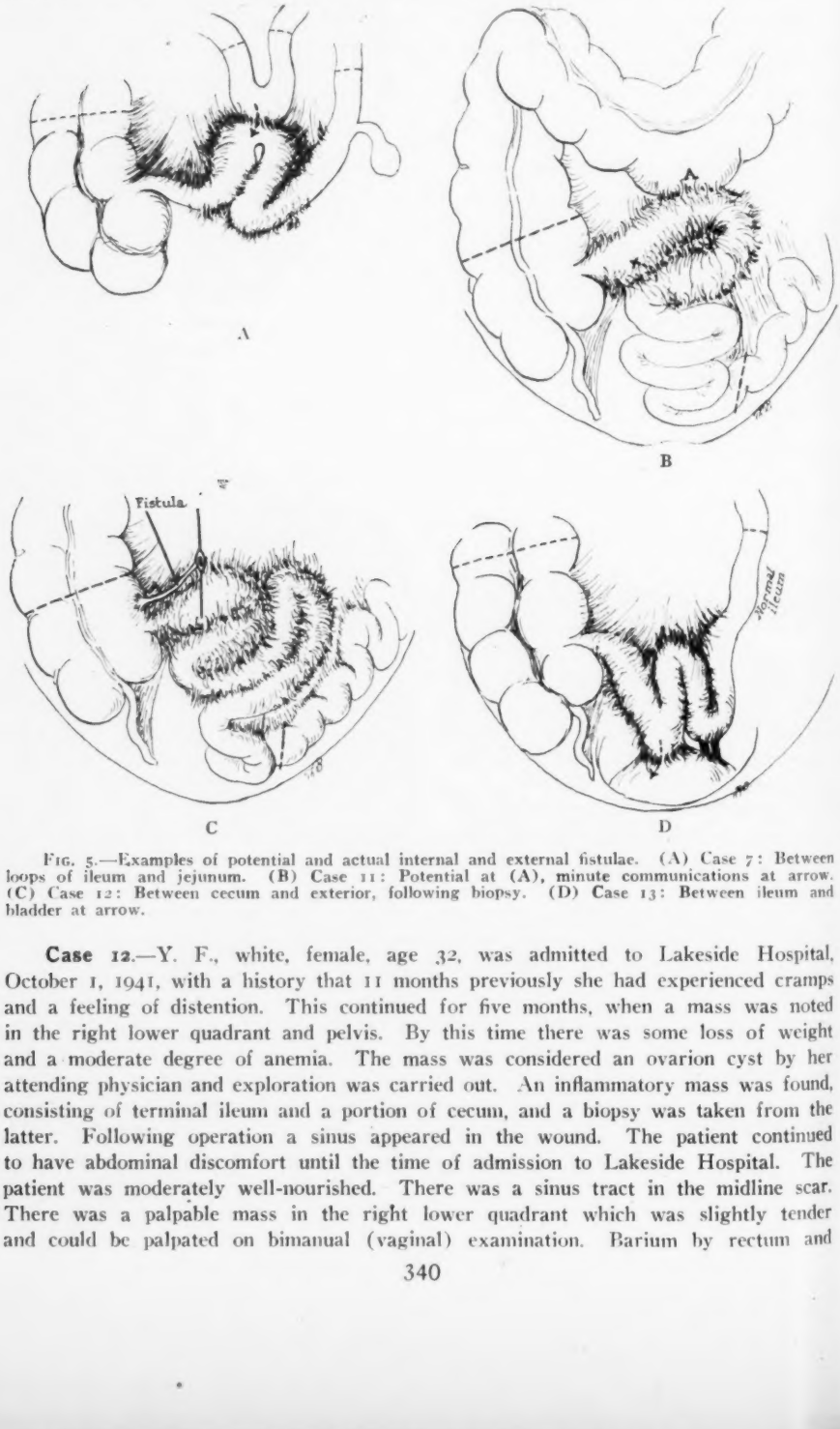


FIG. 5.—Examples of potential and actual internal and external fistulae. (A) Case 7: Between loops of ileum and jejunum. (B) Case 11: Potential at (A), minute communications at arrow. (C) Case 12: Between cecum and exterior, following biopsy. (D) Case 13: Between ileum and bladder at arrow.

Case 12.—Y. F., white, female, age 32, was admitted to Lakeside Hospital, October 1, 1941, with a history that 11 months previously she had experienced cramps and a feeling of distention. This continued for five months, when a mass was noted in the right lower quadrant and pelvis. By this time there was some loss of weight and a moderate degree of anemia. The mass was considered an ovarion cyst by her attending physician and exploration was carried out. An inflammatory mass was found, consisting of terminal ileum and a portion of cecum, and a biopsy was taken from the latter. Following operation a sinus appeared in the wound. The patient continued to have abdominal discomfort until the time of admission to Lakeside Hospital. The patient was moderately well-nourished. There was a sinus tract in the midline scar. There was a palpable mass in the right lower quadrant which was slightly tender and could be palpated on bimanual (vaginal) examination. Barium by rectum and

mouth revealed a lesion which apparently involved not only the terminal ileum but also a portion of the cecum. Laboratory data were essentially negative. There was no anemia at this time. A diagnosis of chronic regional enteritis was made.

The patient was operated upon through a right rectus incision, and the fistulous tract was found to extend to the cecum (Fig. 5C). The terminal 16 inches presented a typical appearance of chronic ileitis, although, for the first time in our series, the process definitely extended beyond the ileocecal valve. The terminal ileum and cecum were resected, with lateral ileocolostomy. Grossly, the specimen showed involvement of a portion of the cecum. Histologic findings were consistent with chronic ileitis and confirmed the involvement of the cecum.

The subsequent course was uneventful. The patient has gained weight, is in excellent health, and has no complaints. *Diagnosis:* Regional ileitis (chronic).

Case 13.—J. K., white, female, age 40, was first admitted to another hospital about 18 months prior to admission to Lakeside Hospital. She complained of lower abdominal discomfort and burning upon urination of several weeks' duration. Operation shortly after admission to the other hospital is said to have revealed extensive inflammation in the pelvis, the abdomen having been closed following exploration. Following the operation urinary symptoms became exacerbated, and some time thereafter the patient noted passage of brown, semisolid material per urethra. At the time of admission to Lakeside Hospital (on the Genitourinary Service), October 13, 1941, the patient had sustained a loss of 20 pounds in weight. It was thought that the patient had an enterovesical fistula. Cystograms were normal, but cystoscopy revealed an inflammatory process involving the posterior wall of the bladder. No fistula was demonstrable. Pelvic examination showed a mass in the right vault extending into the right lower quadrant. A barium meal revealed contrast medium passing into the bladder apparently from the region of the terminal ileum. Thus, an enterovesical fistula was demonstrated, which was thought to be associated with a chronic regional enteritis.

Operation revealed an inflammatory mass in the right lower quadrant consisting of agglutinated folds of the terminal ileum, one of which was firmly adherent to the posterior surface of the bladder (Fig. 5 D). There was no fluid. The bladder was thickened in a manner comparable to the adjacent bowel. The bowel was freed from the bladder and the opening in the bladder was closed. The terminal two and one-half feet of the ileum and the cecum were resected, and a lateral ileocolostomy was done. Grossly, the specimen was typical of chronic ileitis, the process stopping abruptly at the ileocecal valve. Histologic report was consistent with the diagnosis of regional ileitis.

The patient was kept on catheter drainage for one week. The postoperative course was uneventful. The patient has gained considerable weight, has no bladder symptoms, and is progressing satisfactorily to date. *Diagnosis:* Regional ileitis (chronic).

The author wishes to express his appreciation of the assistance given by Dr. Eugene Freedman, of the Department of Roentgenology, and by the Staff of the Institute of Pathology of Western Reserve University. Especial appreciation is due Miss Theodora Bergsland, the artist.

REFERENCES

[1] Bargen, J. A., Wesson, H. R., and Jackman, R. J.: Studies on the Ileocecal Junction (Ileocecus). Surg., Gynec. & Obst., **71**, 33–38, July, 1940.

[2] Crohn, B. B.: Regional Ileitis. Surg., Gynec. & Obst., **68**, 314–321, February 15, 1939.

[3] Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis: A Pathologic and Clinical Entity. J. A. M. A., **99**, 1323–1329, 1932.

[4] Cutler, E. C.: Cicatrizing Enteritis: A Neglected Clinical Entity. Proc. Inter-State Post-Grad. M. A., North America, 1937.

[5] Ginzburg, L., and Garlock, J. H.: Regional Ileitis. ANNALS OF SURGERY, **116,** 906–912, December, 1942.
[6] Holloway, J. W.: Regional Ileitis. Ohio State M. J., **35,** 1059–1061, October, 1939.
[7] Homans, J., and Hass, G. M.: Regional Ileitis: A Clinical, not Pathological Entity. New England J. Med., **209,** 1315–1324, December 28, 1933.
[8] Jackman, W. A.: Localized Hypertrophic Enteritis as a Cause of Intestinal Obstruction: Report of Two Cases. Brit. J. Surg., **22,** 27–32, 1934.
[9] Kantor, J. L.: Regional (Terminal) Ileitis: Its Roentgen Diagnosis. J. A. M. A., **103,** 2016–2020, December 29, 1934.
[10] Koster, H., Kasman, L. P., and Sheinfeld, W.: Regional Ileitis. Arch. Surg., **32,** 789–809, 1936.
[11] Mailer, R.: Acute Regional Ileitis: Report of Two Cases, with Bacteriological Findings. Brit. J. Surg., **25,** 517–529, January, 1938.
[12] Mixter, C. G.: Regional Ileitis. ANNALS OF SURGERY, **102,** 674–694, 1935.
[13] *Idem:* Regional Enteritis. Surg., Gynec. & Obst., **68,** 322–326, February 15, 1939.
[14] Mock, H. E.: Infective Granuloma: Nonspecific Chronic Tumor-like Productive Inflammations of the Gastro-intestinal Tract. Surg., Gynec. & Obst., **52,** 672–689, 1931.
[15] Moschcowitz, E., and Wilensky, A. O.: Nonspecific Granulomata of the Small Intestine. Am. J. M. Sc., **166,** 48–66, 1923.
[16] Reichert, F. L., and Mathes, M. E.: Experimental Lymphedema of the Intestinal Tract and its Relation to Regional Cicatrizing Enteritis. ANNALS OF SURGERY, **104,** 601–616, October, 1936.
[17] Shapiro, R.: Regional Ileitis: A Summary of the Literature. Am. J. M. Sc., **198,** 269–292, 1939.
[18] Smithy, H. G.: Conservatism in the Surgical Management of Acute Regional Enteritis. Surgery, **13,** 122–130, January, 1943.

METASTASIZING INTRACRANIAL TUMORS

KENNETH H. ABBOTT, M.D.
FELLOW IN NEUROSURGERY
MAYO FOUNDATION
AND
J. GRAFTON LOVE, M.D.
SECTION ON NEUROLOGY AND NEUROSURGERY, MAYO CLINIC
ROCHESTER, MINN.

THE OCCURRENCE OF METASTASIS from any primary intracranial neoplasm has been the subject of great interest to both clinicians and pathologists for many decades. Particularly has this been true when metastasis seemed to have occurred outside the central nervous system and its envelopes. To be sure, there have been a number of reports of such metastasis, but considering the many thousands of intracranial tumors that have been studied in many large clinics, these few reports speak well for the rarity of such a metastasizing lesion. In view of this, we wish to report one case in which an intracranial tumor appears to have metastasized to the lungs and hilus nodes.

Case Report.—A male, age 32, registered at the Mayo Clinic, May 20, 1938, because of headaches and vomiting. In January, 1936, he first had noticed a lump in his forehead, very slightly to the left of the midline. He had persuaded his family physician to lance this, but only blood had been obtained. During the next two months the swelling had pulsated and about this time he had found that he could push the lump back into his head, although this had been somewhat painful. In April, 1936, he had been examined elsewhere, and roentgenotherapy had been employed. This had given relief from headaches for about two weeks, they then gradually had returned. In August, 1936, he had received another course of deep roentgenotherapy, with similar results; however, he had been able to get along fairly well until September, 1937, when the headaches had become so severe that he had requested, and had received, another course of treatment. In February and March, 1938, his headaches again had become severe, and at this time they had been associated with frequent vomiting.

When he was first examined at the clinic, neurologic and general physical examinations disclosed the presence of a small mass in the forehead, with obvious erosion of the frontal bone. The optic disks were choked four diopters, about equally in both eyes. The roentgenograms of the skull confirmed the clinical impression of erosion of the frontal bone and, in addition, there was evidence of prolonged increased intracranial pressure.

On May 28, 1938, one of us (J. G. L.) removed a large right parasagittal frontal tumor, which had completely surrounded and invaded the longitudinal sinus. It was necessary to resect the sinus to the entrance of the rolandic veins and to remove a part of the invaded and eroded frontal bone. The tumor weighed 140 Gm., and measured 8 x 7 x 6 cm (Fig. 1). The patient made an uneventful recovery, and when he was dismissed, July 18, 1938, the wound had healed.

He returned to the clinic in November, 1938, because of the presence of a pedunculated growth, two centimeters in diameter, in the anterior end of the operative incision. Radium was applied to this at that time and again in February, 1939, because of recurrence. In spite of this, the patient was able to work from August, 1938, to June, 1939, when headaches again began to be severe. In July, he had a generalized

convulsion, followed five days later by numbness associated with paralysis in the left half of his face. He again returned to the clinic, August 1, 1939, because of the persistence of the facial weakness and of dysarthria. On August 3, 1939, with the use of local anesthesia, a tumor the size of a hen's egg (40 Gm.) was removed from the original site of the neoplasm. He did only fairly well after this procedure and, September 1, 1939, a plastic closure of a cerebrospinal fistula, which had developed soon after the second operation, was performed. He had a very stormy course after this operation, and died, in hyperthermia, September 11, 1939, approximately three years and nine months after he first had noticed the lump in his forehead. A complete necropsy disclosed the defect of the recent removal of the frontal tumor and, in addition, another large residual and recurrent tumor in the right frontotemporal lobes (Fig. 2). There also was evidence of terminal ependymitis and mild meningitis.

FIG. 1.—Tumors removed at the two operations.

Gross examination disclosed nodules of firm gray tissue scattered throughout all lobes of both lungs (Figs. 3 and 4). The hilus nodes also appeared to be infiltrated by small tumor masses. These nodules varied in size up to four millimeters in diameter. There was also pulmonary infarction from arterial emboli.

Histologic examination of the brain tumor disclosed a malignant hemangioblastoma (Grade 3), and all three specimens (two operative and one postmortem) were found to be identical (Figs. 5, 6 and 7). Sections of the miliary nodules in the lungs and hilus nodes disclosed a tumor of identical structure (Fig. 8) to that found in the brain. There was no doubt as to the identity of the tumor.

Sections of the removed tumors and of the residual tumors were examined. The following stains were used: Hematoxylin and eosin, Mallory's phosphotungstic acid stain, Perdrau's silver stain, Cajal's and Hortega's stains, and cresyl violet. The hematoxylin and eosin stain disclosed a tumor made up of small blood vessels, capillaries, sheets, strands and islands of endothelial-like cells. Thin-walled vascular channels lined with endothelial cells frequently were found filled with fat, oval an doccasionally somewhat spindle-shaped, hyperchromatic and foam-like endothelial cells. The nuclei were usually small and the cytoplasm was misty and even foam-like. Mitoses were everywhere abundant and were typically present in the intima of the small proliferating blood vessels (pseudocapillaries). The larger vessels occasionally contained erythrocytes, but many did not.

The tiny tumor nodules found in the lungs, pleura and hilus nodes were discrete, circumscribed masses of cells, with exactly the same characteristics as seen in the intracranial tumor. Examination of sections of the metastatic tumors that had been stained with Perdrau's silver stain revealed the typical vascular reticulin pattern of a hemangioblastoma (Fig. 9) just as it did in the case of sections of the intracranial tumor obtained at operation and at necropsy. Mallory's phosphotungstic acid stain,

FIG. 2

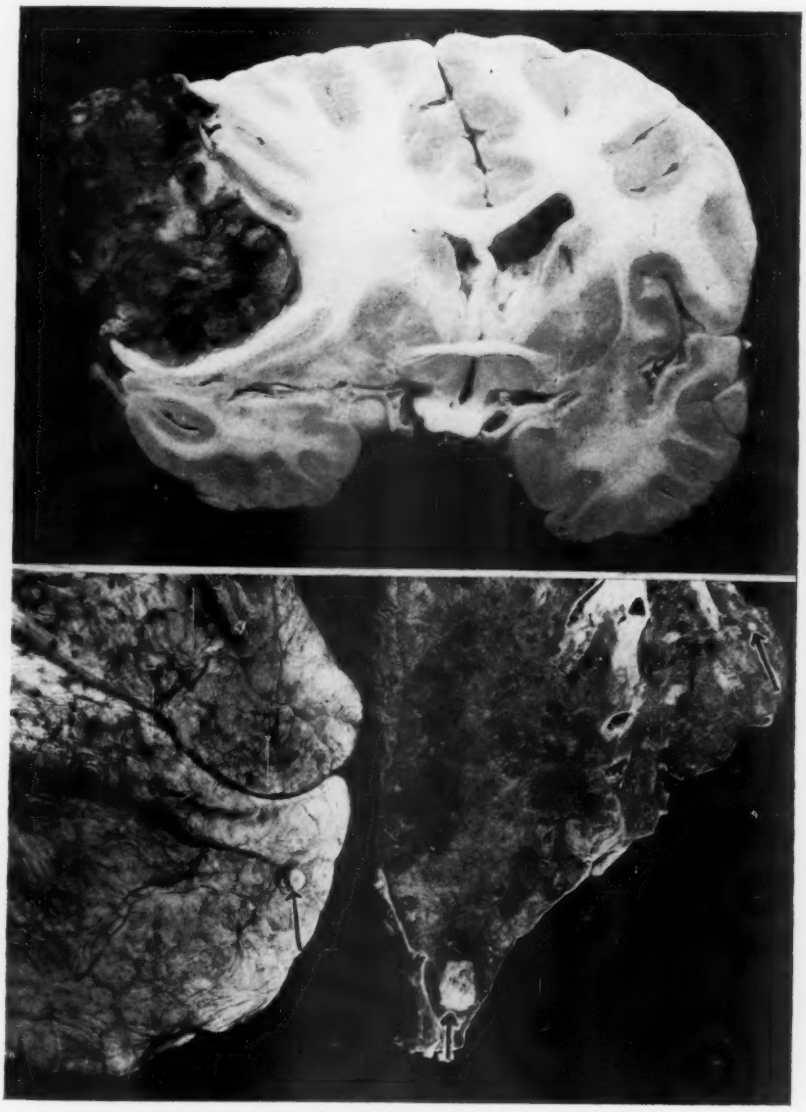


FIG. 3

FIG. 2.—Recurrent hemangioblastoma in coronal section at the level of the optic chiasm.

FIG. 3.—Metastatic tumors in the lung (arrows) from primary intracranial hemangioblastoma.

Cajal's stain and Hortega's stain were only of minor additional value in proving that the tumor was not of glial origin but definitely of vascular origin.

COMMENT

The problem of metastasis encountered any place in the body is not always easily solved, mainly because it is not always possible to be sure which neoplasm is the primary one. This is particularly the situation when one is dealing with metastasis of intracranial tumors. As was, facetiously but correctly, remarked by one pathologist: "The tumor cells do not oblige us with arrows on them showing which way they are going"—certainly one wishes they did.

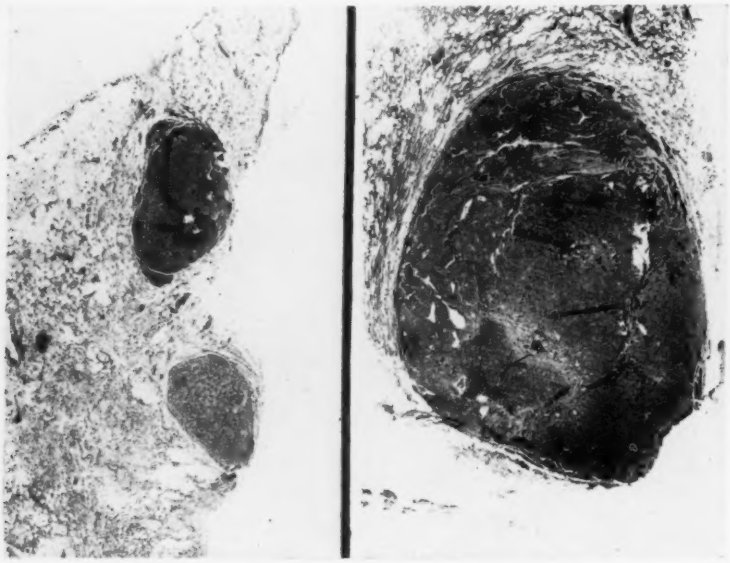
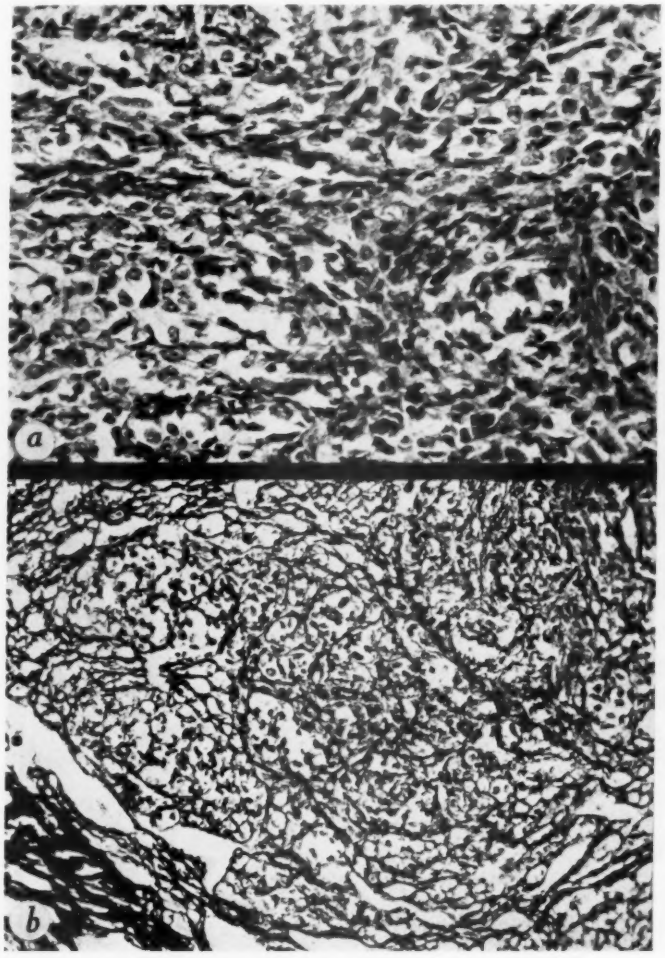


FIG. 4.—Metastatic tumors in the lungs. (×6)

We do not wish to discuss in detail the natural barriers which seem to exist against the process of metastasis of intracranial tumors as these are being extensively investigated by other investigators at the clinic; however, it does seem pertinent to point out the possible rôle which surgical intervention may play in the production of such metastasis. Undoubtedly, in the course of the surgical removal of a neoplasm, venous channels are opened and the intraluminal negative pressure favors the aspiration into their lumina of viable tumor cells. Thus, the tumor cells gain access to the blood stream and are carried to the lungs where they may be "filtered out" in the capillary bed, or the tumor cells, theoretically, could pass on into the arterial blood for dissemination throughout the body. This seems to have been the situation in the metastasizing tumor we have here detailed, although, to be sure, we have not excluded the lymphatics of the scalp as the portal of entry and route of metastasis nor does it seem possible to do so in this instance. Just why in most instances of operative removal of a neoplasm these sup-

posedly "viable" tumor cells do not form metastatic lesions while in rare instances they lodge and grow to reproduce the identical tissue of the primary neoplasm is not known. However, at some future day, this may be explained by certain cytochemical, cyto-electric and physical phenomena which as yet

A



B

FIG. 5.—Sections of hemangioblastoma removed at first operation; A, stained with hematoxylin and eosin (×285); B, stained with Perdrau's silver stain for reticulin. (×150)

remain obscure to investigations. Certainly, nothing is to be gained at this time by pure speculation.

In reviewing the cases reported as cases of metastasizing intracranial neoplasms, we have collected about sixteen. A study of these reports has emphasized in our minds the difficulties one encounters in being certain that a given tumor is primary in the brain or elsewhere. Consequently, we have

divided these cases into three groups: (1) Those cases we do not believe have been shown to be cases of primary tumor of the brain, or we cannot be sure the metastatic tumors, if such they were, came from the brain tumor; (2) cases in which metastasis was questionable, but could possibly have arisen from tumors of the brain; and (3) cases in which metastasis was probable but not entirely certain.

Group 1.—Although it does not seem of much value to review those reports which occurred prior to the beginning of the era of modern methods of staining and histologic diagnosis, it has become necessary to do so, since certain cases have been reported by other authors as examples of this type of neoplastic activity. Among such cases are those of Klebs[6] (1889), and

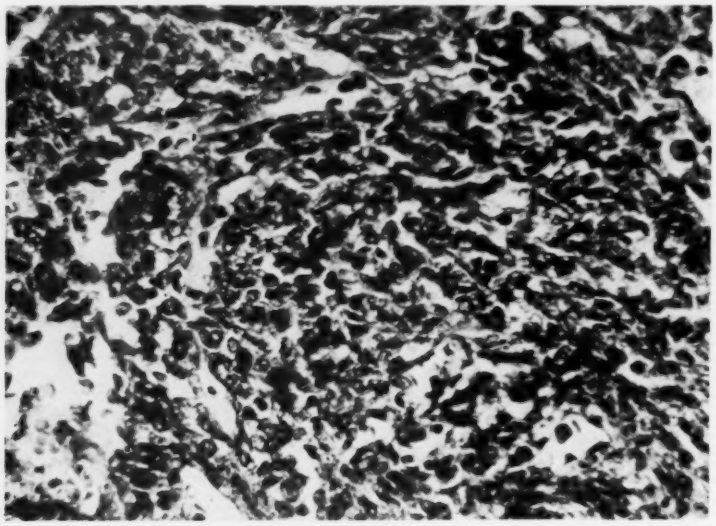


FIG. 6.—Sections of hemangioblastoma removed at second operation, stained with hematoxylin and eosin. (×285)

Lindner[7] (1902). Klebs' report seems to us to have been extremely brief, to have lacked details and photomicrographs or other illustrations. Lindner's case, although reported in more detail, may well have been a case of highly anaplastic primary tumor of the urinary bladder with metastasis to the meninges (carcinomatosis?).

In more recent years, certain reports based on clinical observations certainly cannot be accepted as reports of proved cases. Pendergrass and Wilbur[10] (1928) failed to report any histologic examination of the metastases, and in the report by Rogers, *et al.*[11] (1935), and by Sachs, *et al.*[13] (1936), there were no postmortem studies made to confirm their observations. Although Foot and Zeek[4] reported that they were unable to find any melanotic tumor nodules other than those in the lungs and meninges, it is well known that such tumors metastasize early when the primary neoplasm may be ever so small. Although the patients in these cases may have had a primary

melanoma in the leptomeninges, in view of the many possible primary loci it is certainly open to considerable doubt.

Group 2.—In this group we include those cases in which we believe there is still a reasonable doubt that they fulfill all of the criteria for primary intracranial metastasizing tumors.

It would seem to us that Davis[3] (1928) had fairly well proved his point were it not that his photomicrographs were not too distinct, and it is also noted that Bailey has not accepted this case as a typical case. Wohlwill's[15] (1930) photomicrographs are not at all convincing, although his description would confirm his contention.

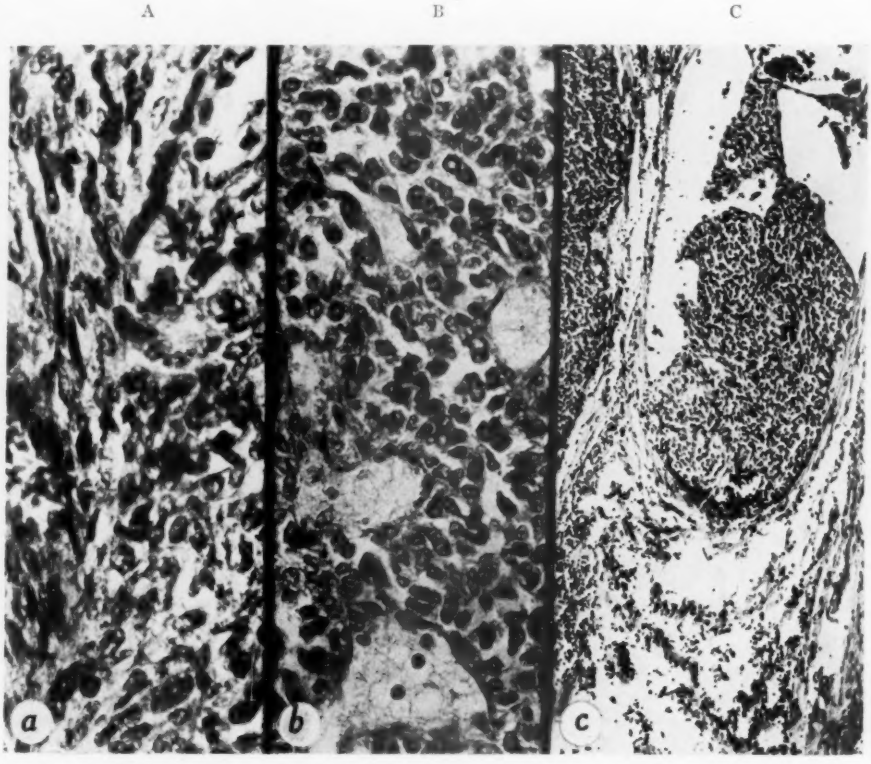


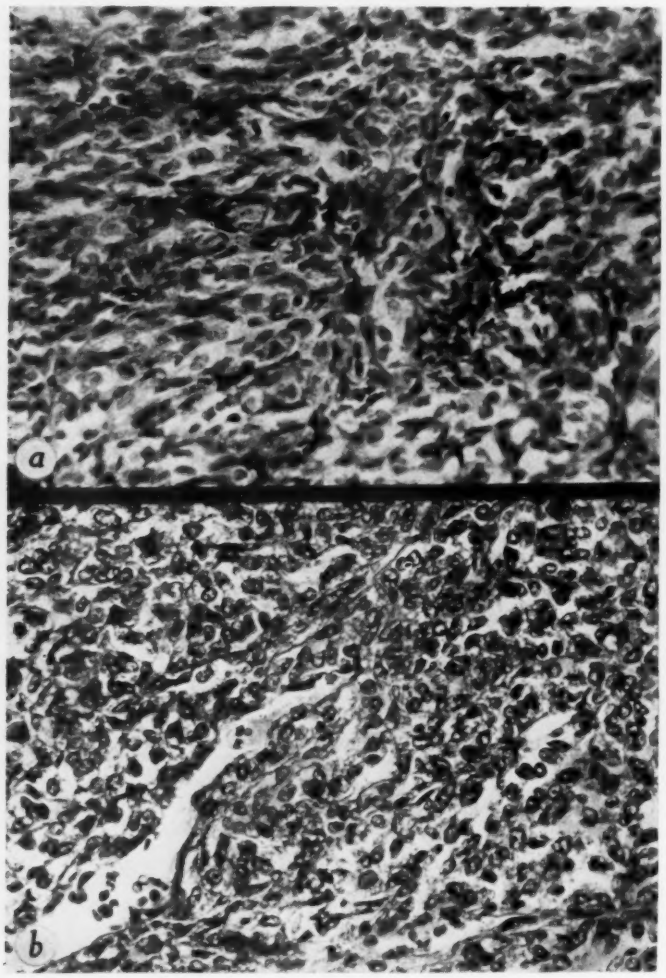
FIG. 7.—Sections of hemangioblastoma obtained at necropsy and stained with hematoxylin and eosin; A, showing sheets and strands of cells with many mitotic figures (×285); B, showing vascular and pseudovascular channels (×250); C, showing tumor tissue partially filling a vascular channel. (×55)

Brandt's[1] (1934) report was given without details and without photographic evidence to support his case. In the case reported by Mittelbach[8] (1935), the patient may well have had a highly malignant primary carcinoma of the lung, as suggested by Fischer-Wasels. For this reason, we are not at all sure he has proven that this is a case of metastasizing intracranial tumor.

Nelson's[9] (1936) report is a little more convincing than some of the others, but certain inaccuracies make us hesitate in accepting his case as a case of medulloblastoma. First of all, the tissue obtained at the time of

the first operation performed at the clinic was examined by Dr. Kernohan, and reported as inadequate for diagnosis. For that reason he did not commit himself any further than to state that the lesion appeared to be a malignant tumor. From the photomicrographs shown in Nelson's article, we agree with Dr. Bailey that it would be difficult to distinguish this tumor from a sarcoma. The question then arises as to the site of the primary neoplasm.

A



B

FIG. 8.—Sections of hemangioblastoma in lung; stained with hematoxylin and eosin (×285); A, arrangement of cells in sheets and strands; B, formation of vascular channels.

The case recently reported by Jurow[5] (1941) is most interesting in that the tumor was not a malignant but apparently a benign meningioma that metastasized to the lung. It seems regrettable that the photomicrographic evidence of the pulmonary lesion was not more convincing.

Russell and Sachs[12] (Case 2) is open to some question since there was an interval of 15 years between the removal of the malignant meningioma and the appearance of the metastases in the lungs, pleura, abdominal lymph nodes and vertebra. Might the patient not have had another primary extracranial tumor which produced these metastases? In spite of the excellent description given by these authors we could not be certain of the nature of the pulmonary lesions from their photomicrographs.

Group 3.—In the third group we have included the report of metastasizing tumors which we feel are, in all probability, excellent examples of primary intracranial tumors which have metastasized outside the central nervous system and its envelopes. In this group we would include the cases of

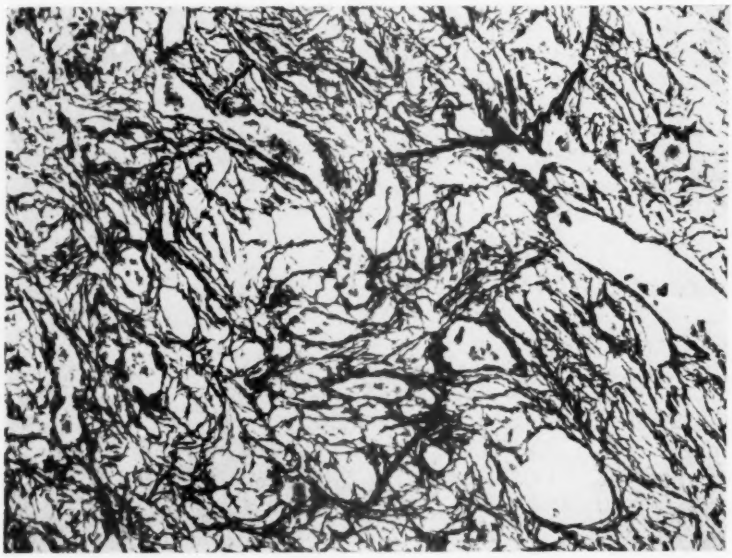


FIG. 9.—Metastatic tumor of lung showing reticulum pattern; stained with Perdrau's reticulin stain. (×150)

(1) Cushing and Eisenhardt[2] (malignant meningioma), Cases 1 and 3 of Russell and Sachs ("fibrosarcoma"—malignant meningioma), and the case which we have just reported (hemangioblastoma).

Another case, that reported by Towne,[14] might well belong in this group were it not for a more strict conception of metastasis. His patient had a malignant meningioma which invaded the inferior longitudinal sinus with extension into the straight, superior, right and left lateral sinuses and down into the internal jugular and innominate veins as far as the upper part of the superior vena cava. It truly was a most remarkable neoplasm. In addition, there was a report of the removal, one year previous to the patient's death, of an "endothelioma of the carotid body." This may or may not have been a metastatic nodule from the primary tumor in the brain or might have been an extension of the tumor through the wall of the left internal jugular vein!

SUMMARY

In the case of metastasizing intracranial hemangioblastoma which we have reported, the patient lived three years and nine months after the first appearance of symptoms, and one year and three months after the first surgical procedure. Sixteen cases of primary intracranial tumors which have been reported as metastasizing outside the central nervous system and its envelopes have been reviewed. Six are not accepted and seven others are accepted as possible cases of metastasizing intracranial tumors, but are open to question. Another three cases are in all probability excellent examples of this type of lesion. To these three cases we have added another.

REFERENCES

1 Brandt, M.: Fünf Fälle mehrfacher Gliome im Grosshirn. Verhandl. d. deutsch. path. Gesellsch., **27**, 39–42, 1934.

2 Cushing, Harvey, and Eisenhardt, Louise: Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End-Results. Springfield, Illinois, Charles C. Thomas, 1938, p. 716.

3 Davis, Loyal: Spongioblastoma Multiforme of the Brain. ANNALS OF SURGERY, **87**, 8–14, January, 1928.

4 Foot, N. C., and Zeek, Pearl: Two Cases of Melanoma of the Meninges, with Autopsy. Am. J. Path., **7**, 605–618, November, 1931.

5 Jurow, H. N.: Psammomatous Dural Endothelioma (Meningioma), with Pulmonary Metastasis. Arch. Path., **32**, 222–226, August, 1941.

6 Klebs, Edwin: Die allgemeine Pathologie. Vienna, Gustav Fischer, 1889, vol 2, p. 628.

7 Lindner, Edwin: Ein Fall von Endotheliom der Dura mater mit Metastase in der Hirnblase. Beitrag zur Histogenese und Differentialdiagnose der Endotheliome. Inaug.-Dissert., Munchen, No. 59, June, 1902.

8 Mittelbach, Maria: Uber Gliome mit Metastasen. Beitr. z. path. Anat. u. z. allg. Path., **95**, 538–572, 1935.

9 Nelson, A. A.: Metastases of Intracranial Tumors. Am. J. Cancer, **28**, 1–12, September, 1936.

10 Pendergrass, E. P., and Wilbur, D. L.: Tumor of the Brain with Widespread Metastases: Report of Two Cases. Arch. Neurol. & Psychiat., **19**, 437–445, March, 1928.

11 Roger, Henri, Alliez, Joseph, and Jouve, André: Syndrome d'adiposité du tronc et de la tête (á type d'adénome basophile hypophysaire de Cushing) avec métastases néoplasiques pulmonaires et rachidiennes. Rev. neurol., **1**, 969–976, 1935.

12 Russell, W. O., and Sachs, Ernest: Fibrosarcoma of Arachnoidal Origin, with Metastases: Report of Four Cases, with Necropsy. Arch. Path., **34**, 240–261, July, 1942.

13 Sachs, Ernest, Rubinstein, J. E., and Arneson, A. N.: Results of Roentgen Treatment of a Series of 119 Gliomas. Arch. Neurol. & Psychiat., **35**, 597–615, March, 1936.

14 Towne, E. B.: Invasion of the Intracranial Venous Sinuses by Meningioma (Dural Endothelioma). ANNALS OF SURGERY, **83**, 321–327, March, 1926.

15 Wohlwill, F.: Zur pathologischen Anatomie der malignen medianen Kleinhirntumoren der Kinder (sog. "Medulloblastome"). Ztschr. f. d. ges. Neurol. u. Psychiat., **128**, 587–614, 1930.

CONSERVATION OF LUNG TISSUE BY PARTIAL LOBECTOMY

MAJOR BRIAN BLADES, M.C., A.U.S.

THORACIC SURGERY SECTION, WALTER REED GENERAL HOSPITAL

WASHINGTON, D. C.

THE TRANSITION of pulmonary anatomy from an academic to an applied subject became complete when the mortality and morbidity of thoracic operations were lowered to about the same order as encountered in operative procedures elsewhere in the body. The lungs, the pulmonary lobes and the various divisions and segments of the lobes have been the objects of intensive and systematic studies by various investigators. The surgical possibilities are becoming more and more apparent as this knowledge increases.

Before anesthetic technics were perfected, assuring the safety of unhurried and precise operating in the open chest, surgeons were forced to place a premium on speed. Pulmonary resections in most cases were accomplished as rapidly as possible by mass ligation of the hilum of the lobe with the aid of a tourniquet. It was necessary, therefore, to sacrifice the entire lobe regardless of the extent of the disease. Even before researches in the surgical anatomy of the lungs eliminated the necessity of mass ligation methods in many cases, it was recognized that the five pulmonary lobes distinguished by more or less constant fissures could not be regarded as the structural units of the lungs based on the distribution of the bronchi and blood vessels. The importance of the lingula of the left upper lobe has been appreciated for many years. And the dorsal divisions of the lower lobes were considered as separate units of the lung by Ewart[1] as early as 1889. In 1934, Nelson[2] suggested that the lungs were made up of eight lobes. Two upper lobes, two middle lobes (the lingula of the left upper lobe was considered the left middle lobe) the dorsal divisions of the lower lobes and the basal divisions of the lower lobes (Fig. 1).

An anatomic approach to pneumonectomy by separate ligation of the structures at the pulmonary hilum was first practiced by Rienhoff,[3] Mason,[4] and Crafoord.[5] The technic was soon adopted widely because the incidence of successful closure of the bronchus was greatly increased. The success of the method stimulated several investigators[6] to study the surgical anatomy of the pulmonary lobes in an effort to determine the feasibility of separate ligation of each anatomic structure when lobectomy is performed. These studies have demonstrated that in many instances, and probably in the great majority of cases, individual ligation of the structures at the roots of the lobes is a feasible procedure. The technic is preferable because the incidence of severe putrid empyemas following mass ligation methods is greatly reduced.

An important contribution by Churchill and Belsey,[7] in 1938, suggested that despite the lack of uniform and well-defined surface markings the bronchopulmonary segments might replace the lobes as the surgical units

of the lungs. They applied the principle of segmental pneumonectomy in resection of the lingula of the left upper lobe (left middle lobe) by removing the posteromedial segment of the lingula and also employed the technic in operations on the dorsal divisions of the lower lobes. Subsequent experiences have demonstrated that it may be possible to conserve important amounts of lung tissue in selected cases by the extirpation of the diseased pulmonary lobules of a diseased segment rather than an entire lobe. The successful application of the principle of partial lobectomy depends upon an intimate knowledge of the structural anatomy of the lung. It is desirable, therefore, to review briefly the various lobes, divisions and segments of the lungs and establish the surgical and pathologic significance of each. In the following discussion of the surgical units of the lung, the nomenclature proposed by Adams and Davenport[8] will be employed.

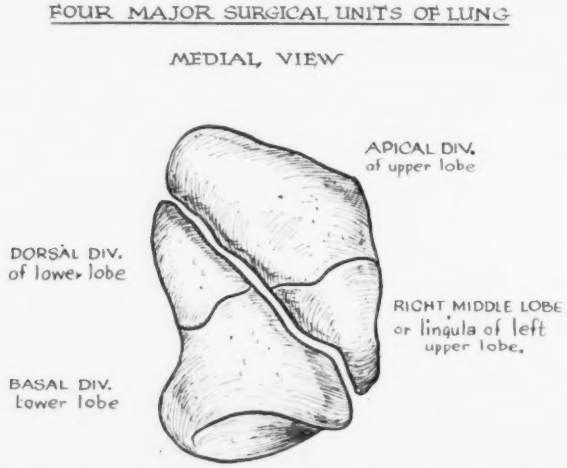
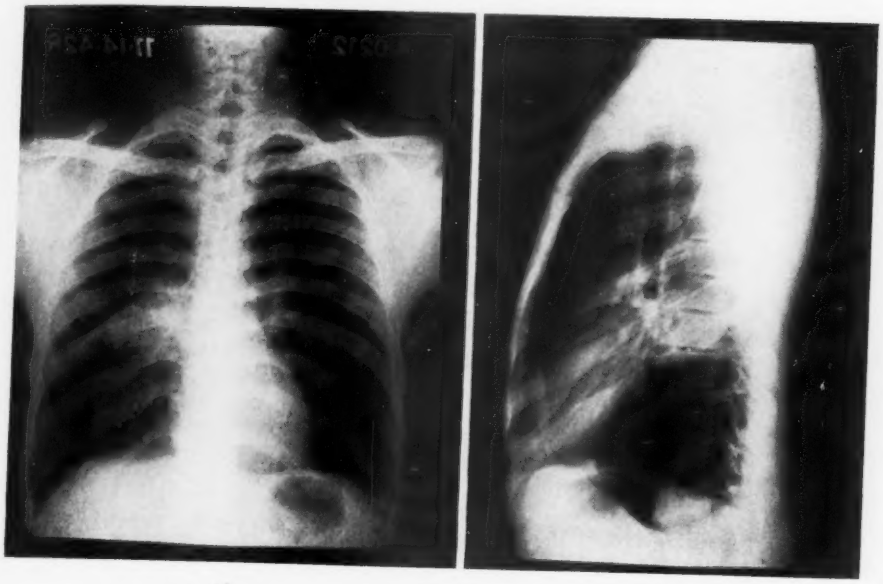

FOUR MAJOR SURGICAL UNITS OF LUNG
MEDIAL VIEW
APICAL DIV. of upper lobe
DORSAL DIV. of lower lobe
RIGHT MIDDLE LOBE or lingula of left upper lobe.
BASAL DIV. lower lobe

FIG. 1.—Diagrammatic representations of the surgical lobes of the lung. Each unit has a separate bronchus and arterial and venous channels accessible for individual ligation technic.

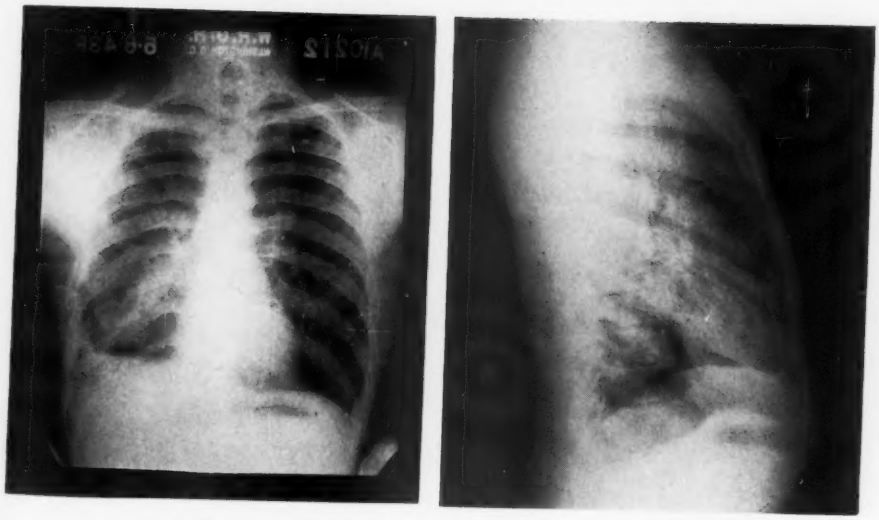
THE STRUCTURE OF THE LOWER LOBE

Both lower lobes are composed of two divisions, namely, the dorsal and basal divisions.

The dorsal division of the lower lobe is such a well-defined and constant structure that it is generally considered as a separate lobe. This division of the lower lobe possesses a definite arterial and venous channel and a separate bronchus. Not infrequently it is separated from the basal portion of the lower lobe by a distinct fissure, and of all the pulmonary segments it is most adaptable to separate removal. Precise localization of the dorsal division segment at operation, even when the superficial markings are absent or incomplete, is not difficult because its bronchus is easily accessible and, by occluding it, a delineating atelectasis of the division can be produced. The dorsal divisions of the lower lobes have special significance both surgically and pathologically since these segments are by far the most



2A



2B

FIG. 2.—A. Roentgenograms of the chest demonstrating a sharply localized lesion of the dorsal division of the right lower lobe.

B. Appearance of the chest after resection of the dorsal division of the lower lobe. The dorsal division which contained a chronic pulmonary abscess was removed alone and the entire basal division of the lower lobe saved.

frequent sites of pulmonary abscess. Involvement of these divisions by bronchietasis is rare, however, despite the predominance of bronchiectatic lesions in the basal segments of the same lobe. It becomes apparent, therefore, that if the disease is sharply localized to either division of the lower lobe the affected portion of the lobe may be removed separately (Fig. 2 A and B).

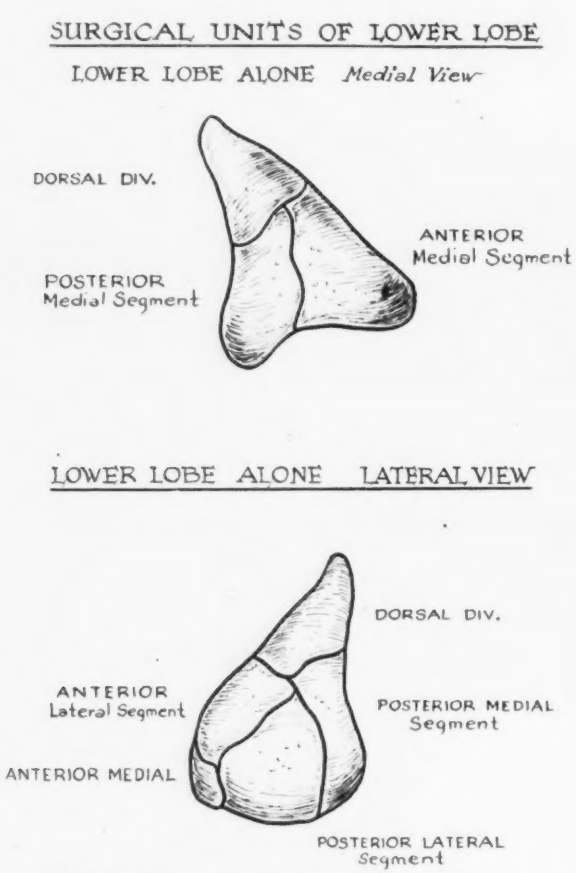


FIG. 3.—Schematic drawings of the lower lobe demonstrating the four segments of the basal divisions.

BASAL DIVISION OF THE LOWER LOBE

The basal division of a lower lobe is divided into four fairly constant segments—anteromedial, posteromedial, anterolateral and posterolateral (Fig. 3). In some cases an attempt to resect any one of the four segments in the basalar division would be impractical and dangerous. The superficial markings on the surface of the lungs are rarely sufficiently clear-cut to distinguish clearly each of the four segments, and inaccurate localization might result, in some instances, in incomplete extirpation of the diseased lung tissue. However, when both of the anterior segments or the posterior segments are

removed there is a sufficient margin of safety to insure complete eradication of a lesion confined to the periphery in an anterior or posterior position. Visualization of the lower lobe bronchus with a bronchoscope will reveal two segmental bronchi, and sometimes all four segmental bronchi can be seen. Adequate bronchography and bronchoscopic examination will establish the anterior or posterior location of the lesion. Not infrequently, one or more of the segments of the basal division will be sharply defined by rudimentary fissures. If preoperative localization places the lesion, usually bronchiectasis, in the well delineated segment, excision of the single segment is safe and advantageous (Figs. 4 and 5).

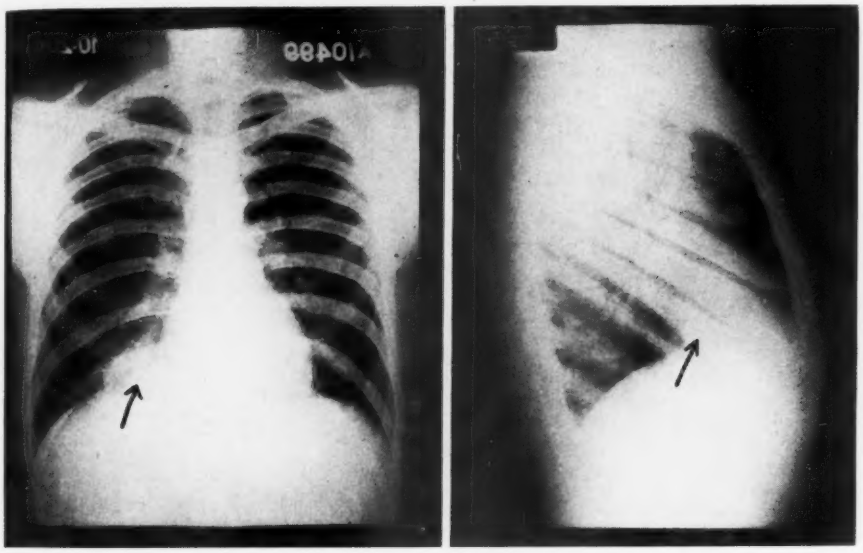


FIG. 4A.—Roentgenograms of the chest showing a sharply localized peripheral lesion of the anteromedial segment of the right lower lobe.

THE MIDDLE LOBES

For surgical purposes, the lingula of the left upper lobe may be regarded as the left middle lobe. Except for minor anatomic variations, and perhaps embryonic differences, the lingula is comparable in every respect to the right middle lobe. Both pathologically and surgically they are of the same significance. For example, the lingula is involved in more than 60 per cent of cases of bronchiectasis of the left lower lobe. The same condition is true for the right middle lobe when the right lower lobe is bronchiectatic. The boundaries of the lingula and the right middle lobe are easily identified and their bronchi are of sufficient lengths to allow individual management. They both are composed of two segments, the anterolateral and posteromedial.

Segmental pneumonectomy on the lingula division has been performed successfully by Churchill,[7] with removal of the posteromedial segment alone. It is questionable, however, that individual resection of either of the segments of the right middle lobe would be advisable. The segments on the right are

difficult to identify and little lung tissue would be saved. Lesions localized in the right middle lobe should, therefore, be removed by complete lobectomy. In this connection it should be stated that if there is any question concerning the amount of lung tissue to be excised the surgeon is obligated to error on the radical side. Inadequate extirpation of the diseased tissue will cast disrepute on a principle that is sound when employed properly.

FIG. 4B.—Bronchogram demonstrating amputated bronchus to the anteromedial segment. The patient was suffering from intractable hemoptysis originating from localized bronchiectasis of the anteromedial segment of the lobe. The remainder of the lobe was conserved by partial lobectomy. The patient is cured, and is now on active military duty.

THE SURGICAL UNITS OF THE APICAL DIVISION OF THE UPPER LOBES

The apical divisions of the upper lobes are divided into four segments—anterosuperior, posterosuperior, anterolateral and anteroinferior.

Since tuberculosis is the predominant disease of the upper lobes, local excision of lung tissue of the anterosuperior or posterosuperior segments will not be indicated in many cases. There are, however, occasional instances when partial lobectomy of the upper lobe will obviate the necessity for total pneumonectomy. For example, bronchiectasis of the anteroinferior or lateral segments of the upper lobes may be found in association with middle lobe disease on the same side. The remainder of the upper lobe can be

saved by resection of the involved segment. Another important indication for the excision of a diseased segment in the upper lobe will sometimes be encountered in suspected bronchiogenic tumor cases. In sharply localized peripheral masses from which tissue cannot be obtained through the bronchoscope for microscopic study, excision of the local lesion should be performed before a radical operation is undertaken. Gross examination and rapid microscopic studies of the tissue may prevent the calamity of unnecessary pneumonectomy. Inspection of the surface of the lungs and palpation through intact lung tissue while usually adequate, is not wholly reliable. In

FIG. 4C.—Photograph of operative incision two weeks after the partial lobectomy.

our own experience, a case which presented all of the characteristic clinical features of peripheral bronchiogenic carcinoma, except a visible tumor on examination with the bronchoscope, was subjected to exploratory thoracotomy with the intention of performing a pneumonectomy. Inspection and palpation of the lung in the operating room strengthened the opinion that the lesion was a carcinoma. Local resection of the involved lung tissue and rapid histologic study, however, revealed that the lesion was inflammatory.

The hazards of exploratory thoracotomy are so insignificant that there should be no hesitation in recommending it if other diagnostic procedures have failed to establish the nature of an intrathoracic mass. The application of this principle will undoubtedly lead to earlier diagnosis and increasing numbers of successful operations for peripheral lung tumors. If, however, there is any question concerning the nature of the disease, failure to resect the local lesion before a radical operation is undertaken will constitute a grave error in judgment (Fig. 6 A and B).

REQUIREMENTS FOR PARTIAL LOBECTOMY

Certain requirements must be fulfilled if the principle of lung conservation by partial lobectomy is to be successful: First, all of the diseased pulmonary lobules must be identified and extirpated; second, the major bronchi and vessels of adjacent segments must be left intact; and third, the satisfactory repair of the raw surface of incised lung tissue must be accomplished.

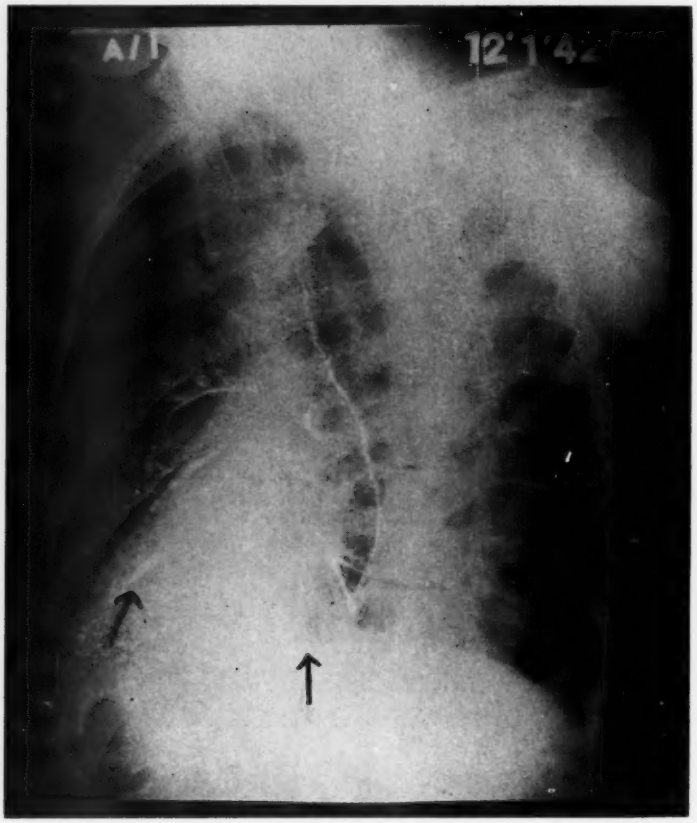


FIG. 5A.--Bronchogram showing sharply localized bronchiectasis of the lingula of the left upper lobe and the posteromedial segment of the left lower lobe.

Precise preoperative localization of the disease with an accurate appraisal of its boundaries in terms of bronchopulmonary segments, can be accomplished by conventional roentgenograms, properly prepared bronchograms, and examinations with the bronchoscope. This information, combined with actual inspection and palpation of the lungs when the operation is undertaken, will usually localize the diseased lobules in a satisfactory manner. When the dorsal divisions of the lower lobes or the lingula of the left upper lobe are the objects of surgical attack, temporary occlusion of the bronchus to the division will positively identify its boundaries. If the bronchus to a segment is not easily accessible, and it is impractical to produce atelectasis

to delineate the segment, rapid variations in the intratracheal pressure will often aid in outlining the various segments (Fig. 7 A, B and C). Careful inspection of the lung surface not infrequently will reveal rudimentary fissures which become more apparent during inflation and deflation of the lung. It is our impression that often the diseased segments fail to inflate as rapidly as adjoining normal segments.

Transillumination of the inflated lung tissue at the operating table will, we believe, furnish another valuable aid in localizing small sharply localized lesions. Further experience with this method will be necessary before its accuracy can be evaluated.

When a palpable mass is encountered the simple expedient of excising it with a margin of healthy tissue is permissible. This practice will not, however, eliminate the necessity of careful and complete preoperative localization of the disease.

There is little danger of injuring the bronchi and blood supply of adjacent lung tissue when a diseased segment of a lobe is extirpated. The rich pulmonary blood supply limits the possibilities of producing gangrene of lung tissue to ligation of major vessels or to the injudicious use of encircling ties which will occlude the blood supply to distal lobules. A comparable margin of safety is also present in the bronchial tree. Many of the limbs of the tree can be destroyed so long as the trunk is preserved. Excision of the periphery of a contiguous segment will, therefore, cause no permanent damage.

If the principle of partial lobectomy for the conservation of healthy lung tissue is generally adopted, it is safe to assume that various refinements in operative technic will develop. The method I shall describe is offered as one which has proved satisfactory in a series of eight cases (removal of the lingula not included). There were no deaths and only one case was complicated by postoperative empyema. Assessment of any influence on the immediate mortality of the procedure compared to total lobectomy, however, must await further experience.

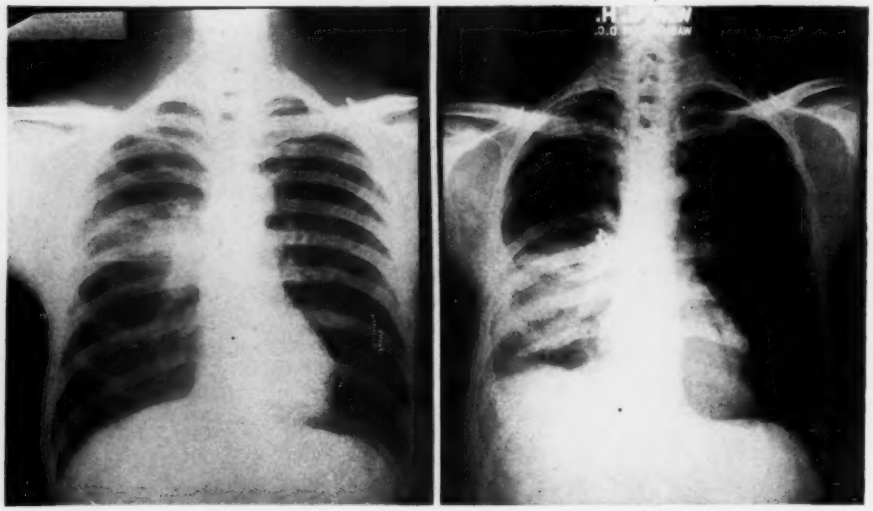
FIG. 5B. — Photograph of patient 18 days after lingulectomy and partial lower lobe lobectomy. Despite the rather minimal amount of bronchiectatic dilations the patient was incapacitated by a chronic productive cough before the operation. The soldier has returned to duty.

Morbidity and empyema become almost synonymous in a consideration of lung operations and infections of the pleura, and usually result from bronchial fistula. Thoroughly satisfactory results in partial lobectomy will depend, therefore, upon the ability of lung tissue to heal after incision and suture. Experimental observations, by Olch and Ballon,[9] indicate that healing and scar tissue formation in the lungs is similar to that elsewhere in the body. There is, in addition to laboratory observations, ample clinical evidence to prove that the pulmonary parenchyma heals readily provided the

blood supply is not destroyed and the incision is made through healthy tissue. The bronchi in the peripheral portion of the lungs are of small caliber and, unless they become fixed to the chest wall, permanent closure of the divided bronchi can be anticipated in most cases. It is in this connection that the use of a pleural graft, which will be described, is probably of great value.

OPERATIVE TECHNIC

No comment is necessary on the technic of lingulectomy. The method described by Churchill and Belsey[7] is entirely satisfactory and generally accepted. Excision of the dorsal division of a lower lobe can usually be



6A 6B

FIG. 6A.—Preoperative roentgenogram of a case which was considered to be bronchiogenic carcinoma.

B. Roentgenogram of chest ten days after local resection of an inflammatory lesion. Total pneumonectomy was avoided by partial lobectomy. The haziness in the lower right chest represents a small amount of fluid and thickened pleura; the result of the thoracotomy.

effected through relatively avascular lines of cleavage after the bronchus and blood vessels are identified and secured. When the bronchus is occluded the line of demarcation between the basal and dorsal divisions will be sharply defined and the incision through the lung tissue made at this proper level. Partial excision of the basal division of a lower lobe, however, necessitates incisions through rather thick, vascular lung tissue. Extirpation of the diseased lobules in this location may be accomplished by placing one small hemostat at the desired position and incising the tissue below the level of the instrument. The bleeding vessels in the unclamped cut-surface of the tissue to be removed are seized separately to mark their exact positions. After the division of approximately one inch of lung tissue the line of incision is approximated and the positions of the vessels held by the proximal clamp are determined. These vessels are controlled by suture ligatures before the clamp is removed. By repeating this maneuver, the

A B C

FIG. 7.—A. Photograph of delineating atelectasis of antero-inferior segment of the upper lobe produced by rapid inflation and deflation of the lobe.

B. Atelectasis of the dorsal division of the lower lobe produced by occluding the bronchus to the division.

C. The basal division of the lower lobe after occlusion of the basal division bronchus. Note the enormous difference in the size of the divisions when they are inflated and when they are atelectatic.

segment or desired amount of lung tissue is excised. When the hemostat is removed, oozing from the cut-surface, or a vessel which has not been secured by the suture ligatures, is controlled by a few interrupted sutures of fine absorbable material. The raw cut-surface of lung parenchyma is then covered with a large graft of parietal pleura, which is obtained from the chest wall (Fig. 8).

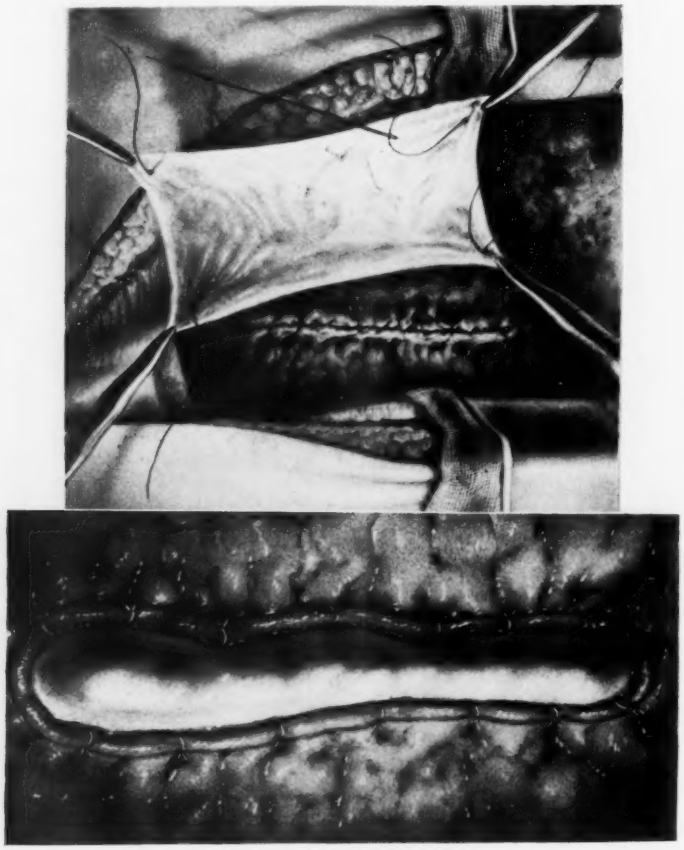


FIG. 8.—Drawings of pleural graft covering the line of incision through the lung tissue. Parietal pleura from the chest wall can be removed easily for this purpose.

Incision of the lung tissue by electrosurgical methods might be advantageous. This technic, however, must wait for an entirely satisfactory non-explosive anesthetic agent. The application of clamps across the lung tissue is admittedly crude, but if the instruments are removed quickly the rich blood supply of the lung apparently prevents permanent damage to adjacent lobules.

It must be emphasized that partial lobectomy should be reserved for suitable cases. The lesion must be peripheral and preoperative localization must coincide precisely with the location of the diseased lobules when the

lung is exposed at the operating table. Finally, if there is any question concerning adequate extirpation of the lesion by partial lobectomy, complete lobectomy should be undertaken. If these precautions are observed important amounts of lung tissue may be conserved successfully in selected cases.

REFERENCES

1 Ewart, William: The Bronchi and Pulmonary Blood Vessels. London, 1889, J. A. Churchill.

2 Nelson, H. P.: Postural Drainage of Lungs. Brit. M. J., **2**, 251, 1934.

3 Rienhoff, W. F., Jr.: Pneumonectomy: A Preliminary Report of the Operative Technique in Two Successful Cases, Bull. Johns Hopkins Hosp., **53**, 390, 1933.

4 Mason, G. A.: Extirpation of Lung (Hunterian Lecture Abridged). Lancet, **1**, 1047, 1936.

5 Crafoord, Clarence: On the Technique of Pneumonectomy in Man. Acta Chir. Scandinan., **81**, Suppl. 54, Stockholm, 1937.

6 Blades, B., and Kent, E. M.: Individual Ligation Technique for Lower Lobe Lobectomy. The Jour. of Thoracic Surg., **10**, 84, 1940.

7 Churchill, E. D., and Belsey, R.: Segmental Pneumonectomy in Bronchiectasis. ANNALS OF SURGERY, **109**, 481, 1939.

8 Adams, Ralph, and Davenport, Lourey T.: Bronchography. J. A. M. A., **118**, 106, 1942.

9 Olch, I. Y., and Ballon, H. C.: Experimental Abscess of Lung Following Ligation of Pulmonary Artery and Incision and Suture of Pulmonary Parenchyma. Arch. of Surg., **19**, 1586–1594, December, 1929.

METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTRO-INTESTINAL TRACT*

X—HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CANCER

IRVING ARIEL, M.D.,† PAUL E. REKERS, M.D.,
G. T. PACK, M.D., AND C. P. RHOADS, M.D.
NEW YORK, N. Y.

FROM THE MEMORIAL HOSPITAL FOR THE TREATMENT OF CANCER AND ALLIED DISEASES, NEW YORK, N. Y.

PATIENTS with gastric cancer frequently present varying degrees of emaciation which conceivably are due to a disturbed fabrication of protoplasm. Since that function is dependent upon proper protein synthesis, it is important to ascertain whether patients with gastric cancer ingest an inadequate amount of protein or have some abnormality of its metabolism.

There is considerable evidence to show that when the tissue protein stores are depleted, the serum protein levels decrease.[1] Hemoglobin synthesis, nevertheless, may continue even during a period of negative nitrogen balance and at the expense of serum protein formation.[2] Hence, were protein synthesis impaired in patients with gastric cancer, they should have a high incidence of hypoproteinemia and anemia. A study, therefore, was made to determine that incidence, and to ascertain if possible the cause.

CLINICAL MATERIAL AND METHODS

The incidence of hypoproteinemia and anemia was determined among:

1. Twenty-five healthy adults of from 20 to 65 years old.
2. Ninety-seven patients with gastric cancer.
3. Twenty-three patients with non-neoplastic gastric disorders. Seventeen had gastric ulcers and six had atrophic gastritis. All had anorexia and a diminished dietary intake.
4. Twenty-one patients with nonspecific oral leukoplakia.
5. Twelve patients who had had a gastric carcinoma removed from three months to ten years before the present study.
6. Finally, a last group of ten patients with gastric cancer, who were studied in particular to ascertain whether or not they excreted in their feces an abnormally great amount of nitrogen.

No patient was studied until he had taken an adequate diet for at least two days, and was considered to be in a satisfactory state of hydration. All blood samples were obtained when the patients were in a fasting state.

The chemical methods employed in the present study have been described in previous communications of this series.[3, 4]

Anemia was considered to exist when the red blood cell count was less

* The authors gratefully acknowledge the grant made by the National Cancer Institute.

† Trainee in Diagnosis and Treatment, National Cancer Institute.

than four million and the hemoglobin less than 80 per cent (Sahli scale, 14.5 Gm. hemoglobin = 100 per cent). Concentrations of total serum protein of less than 6.6 Gm., albumin of less than 4.0 Gm., and serum globulin of less than 2.0 Gm. per cent were considered abnormally low.

The criteria used to establish the existence of a dietary deficiency were: (a) A history of decreased food intake as obtained from the patient or his family; or (b) observation of the dietary intake of the patient while in the hospital.

Bleeding from the gastro-intestinal tract was established by: (a) A history of melena or hematemesis within six months prior to study; or (b) the demonstration of blood in the stools or gastric content after the patient had taken a meat-free diet for three days.

RESULTS

A. THE EXISTENCE OF HYPOPROTEINEMIA AND ANEMIA IN NORMAL ADULTS AND IN PATIENTS WITH CARCINOMA OF THE STOMACH

1. *Normal Adults.*—The total serum protein concentrations of 25 normal adults ranged from 6.6 to 7.8, and averaged 7.1 Gm. per cent. Their red blood cell counts ranged from 3.8 to 5.4, and averaged 4.6 millions per mm.,[3] and the hemoglobin concentrations varied from 76 to 106, and averaged 91 per cent. By the criteria used, then, only one of the 25 individuals was anemic and none were hypoproteinemic (Table I).

TABLE I

THE INCIDENCE OF DIETARY DEFICIENCY, HYPOPROTEINEMIA, AND ANEMIA IN THE GROUPS OF PATIENTS STUDIED

Subjects	Per Cent on Inadequate Diet	Serum Protein Gm. Per Cent		Patients with Hypoproteinemia Per Cent	Hemoglobin Per Cent		Patients with Increased Hb. Concentrations Per Cent	R.B.C. mil./mm^3		Patients with Decreased R.B.C. Per Cent
		Range	Average		Range	Average		Range	Average	
25 normal adults	0	6.6–7.8	7.1	0	76–106	91	4	3.8–5.4	4.6	4
97 patients with gastric cancer	79	3.9–8.0	6.2	59	33–100	70	70	1.4–4.8	3.5	73
23 patients with nonneoplastic gastric disorders	100	6.05–7.15	6.6	35	67–99	83	22	3.7–5.2	4.2	22
21 patients with oral leukoplakia	33	6.6–8.5	7.6	0	78–105	94	7	3.8–5.1	4.7	7
12 patients who had gastric cancer resected	25	6.7–8.1	7.3	0	63–87	75.5	25	3.0–4.8	4.4	25

2. *Patients with Gastric Carcinoma.*—The results of studies on 97 patients with gastric carcinoma were in sharp contrast to those in normal individuals.

(a) *Serum Protein.*—Fifty-nine per cent were hypoproteinemic. Their serum levels ranged from 3.9 to 8.0, and averaged 6.2 Gm. per cent (Table I).

Of these 97 patients, the albumin and globulin concentrations were determined in the serum of 38. In these, the concentrations of albumin ranged from 2.8 to 4.9, and averaged 3.7 Gm. per cent, while the concentrations of globulin varied from 1.2 to 3.0, and averaged 2.1 Gm. per cent. Of those patients with hypoproteinemia, in 73 per cent that abnormality was due to a decreased concentration of the albumin fraction alone.

(b) *Anemia.*—Seventy per cent of the 97 patients had abnormally low hemoglobin concentrations, and 73 per cent abnormally low red cell counts. The hemoglobin concentrations ranged from 33 to 100, and averaged 70 per cent. The red cell counts ranged from 1.4 to 4.8, and averaged 3.5 million per mm.^{3} The anemia was macrocytic in 37 per cent, and microcytic only in nine per cent.

B. THE MOST OBVIOUS EXPLANATIONS FOR THE EXISTENCE OF HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CARCINOMA WERE CONSIDERED TO BE:

1. *Dietary Deficiency.*—Since it has been well established that the fabrication of hemoglobin and serum protein can be influenced by dietary factors,[2] the dietary habits of the patients with gastric carcinoma were studied.

Twenty of the 97 patients with gastric carcinoma apparently had ingested adequate diets, yet 60 per cent of these were hypoproteinemic, and 85 per cent were anemic (Table II). The remaining 77 patients had taken deficient diets, and 61 per cent were hypoproteinemic and 68 per cent were anemic. Hence, no correlation could be found between the existence of dietary deficiency and that of hypoproteinemia or anemia.

TABLE II

THE RELATIONSHIP OF DIETARY DEFICIENCY TO THE OCCURRENCE OF HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CANCER

Number of Patients	Per Cent with Hypoproteinemia	Per Cent with Anemia
20 with adequate diets	60	85
77 with deficient diets	61	68

Although the evidence at hand indicates that the ingestion of inadequate diets could not explain the high incidence of hypoproteinemia and anemia in patients with gastric carcinoma, one could not be satisfied that the normal values used for comparison were valid controls, since the normal subjects differed considerably in age and in economic and dietary background from the patients with gastric carcinoma. It was important, therefore, to control these factors further.

Accordingly, the incidence of hypoproteinemia and anemia were determined in two other groups of patients, one with benign gastro-intestinal disorders and the other with oral leukoplakia. The patients of these groups were of an age, and dietary and economic background, similar to those with carcinoma of the stomach.

In six patients with atrophic gastritis and 17 with gastric ulcer, hypo-

proteinemia existed only in 35 per cent and anemia in 22 per cent, although all of the 23 patients had taken grossly inadequate diets (Table I). Likewise, of 21 patients with oral leukoplakia, 33 per cent had been on grossly deficient diets, yet none had hypoproteinemia and only seven per cent were anemic. A comparison of these findings with those of patients with gastric carcinoma seemed to provide sufficient proof that the factors of age, dietary and economic background of the latter group were not responsible for their high incidence of hypoproteinemia and anemia.

2. *Blood Loss.*—Since the fabrication of hemoglobin frequently may be at the expense of serum protein formation, the continual loss of blood from the gastro-intestinal tract conceivably might have caused both the anemia and hypoproteinemia in patients with gastric carcinoma. Of 86 patients in whom the incidence of bleeding into the gastro-intestinal tract was determined, blood loss was noted in 39. In this group, 59 per cent were hypoproteinemic, 72 per cent anemic, and 31 per cent had macrocytosis despite the fact that they had chronically lost blood. In the remaining 47 patients, who had not sustained any blood loss, 67 per cent, nevertheless, were hypoproteinemic, 74 per cent were anemic, and 43 per cent had macrocytosis (Table III). Hence, there was no significant difference in the incidence of hypoproteinemia and anemia between the group of patients that had gastro-intestinal bleeding and the group that did not.

TABLE III

THE RELATIONSHIP OF CHRONIC BLOOD LOSS TO THE OCCURRENCE OF HYPOPROTEINEMIA, ANEMIA AND MACROCYTOSIS IN PATIENTS WITH GASTRIC CANCER

Number of Patients	Per Cent with Hypoproteinemia	Per Cent with Anemia	Per Cent with Macrocytosis
39 with chronic blood loss	59	72	31
47 without chronic blood loss	67	74	43

3. *The Presence of the Tumor.*—The possibilities next were considered that patients with gastric carcinoma frequently had hypoproteinemia and anemia because their gastric lesions either interfered with digestion and absorption of food or induced a metabolic abnormality which impaired protein fabrication.

Measurements were made of the protein ingested and nitrogen excreted in the stools of ten patients bearing gastric carcinoma.[5] All ten were found to excrete in their feces normal amounts of nitrogen (Table IV). This observation would indicate that patients with gastric cancer did not have any disorders concerned with the digestion of proteins or the amount of digested protein that could be absorbed.

Finally, none of a group of 12 patients who had undergone successful removal of their gastric tumors from three months to ten years before this study were found to have hypoproteinemia, but 25 per cent still were anemic (Tables I and V). No correlation could be found between the persistence of anemia and the interval which elapsed from the time of resection. The fact that this group of patients no longer were hypoproteinemic suggests that the presence of the gastric carcinoma had initiated a disorder which prevented

the normal fabrication, utilization, or distribution of serum proteins. Evidently, the impaired fabrication of hemoglobin is less often reversible.

SUMMARY

The majority of patients with gastric carcinoma studied were both hypoproteinemic and anemic. The ingestion of deficient diets and the chronic loss of blood were not sufficient explanation for the high incidence noted.

TABLE IV

THE EXCRETION OF NITROGEN IN THE FECES OF PATIENTS WITH GASTRIC CANCER

Patient	Average Dietary Protein N. Gm. Per Day	Average Fecal N. Gm. Per Day	Average Fecal N. Percentage of Protein Nitrogen Ingested
S. S.	9.2	0.4	3.8
R. S.	13.5	2.2	6.2
M. M.	14.6	1.1	7.3
L. T.	17.6	0.5	3.0
G. C.	30.6	1.7	5.5
R. M.	19.6	1.0	5.3
H. P.	26.4	2.1	8.55
P. T.	15.6	1.0	6.7
A. A.	16.6	0.8	4.7
I. Z.	18.5	1.1	5.9

TABLE V

THE OCCURRENCE OF HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WHO HAD HAD A GASTRIC CARCINOMA RESECTED

Patient	Diet	Survival Period Postoper. Months	Serum Protein Gm. Per Cent	R. B. C. Mil. mm.^{3}	Hemoglobin Per Cent	M. C. V. Cu. Micra.
L. B.	Adequate	60	6.7	3.8	72	89
N. C.	Adequate	60	8.1	4.1	81	80
J. C.	Deficient	12	6.9	3.5	73	90
W. E.	Adequate	6	7.3	4.1	80	96
E. P.	Deficient	3	6.7	3.0	48	81
K. T.	Adequate	96	7.0	4.4	88	90
J. Z.	Adequate	120	7.1	4.2	83	90
A. S.	Adequate	60	7.5	4.2	83	90
M. I.	Adequate	16	7.9	4.8	98	90
H. S.	Adequate	40	7.1	4.5	90	95
P. S.	Deficient	31	7.6	4.5	92	90
A. J.	Adequate	15	7.2	4.4	88	85

Furthermore, the observation that patients bearing a gastric cancer excreted normal amounts of nitrogen in their feces argued against the possibility that the hypoproteinemia and anemia were due to a malabsorption and maldigestion of dietary protein. However, the resection of the tumor apparently improved the ability of the patients to fabricate protein, and suggested that the presence of the carcinoma had induced the existence of some metabolic abnormality which impaired protein formation. The rôle of infection around the tumor could not be ascertained in this investigation.

The cause of anemia in patients with gastric cancer certainly is not clear. It has been demonstrated in this study that the incidence and

severity of anemia is no greater among the group who had manifested gastro-intestinal bleeding, than among those who did not. Moreover, it has been the experience in this hospital that the long-continued administration of large amounts of ferrous salts and liver concentrates has not significantly affected the blood picture of patients with gastric cancer. The coexistence of hypoproteinemia and anemia in these patients, however, does suggest that the latter abnormality may be due to an impaired protein metabolism.

CONCLUSIONS

1. Fifty-nine per cent of patients with gastric carcinoma studied had hypoproteinemia, and about 70 per cent anemia. No correlation could be found between the occurrence of these abnormalities and the incidence of deficient dietary intake or chronic blood loss from the gastro-intestinal tract.

2. The incidence of hypoproteinemia and anemia is considerably less in patients who have had their gastric carcinoma removed surgically.

3. The possibility is suggested that the hypoproteinemia and anemia in patients with gastric carcinoma is due to a defective fabrication of proteins.

REFERENCES

[1] Sachar, L. A., Horvitz, A., and Elman, R.: Studies in Hypoalbuminemia Produced by Protein Deficient Diets. I. Hypoalbuminemia as a Quantitative Measure of Tissue Protein Depletion. J. Exp. Med., **75**, 453–459, 1942.

[2] Whipple, G. A.: Hemoglobin and Plasma Proteins: Their Production, Utilization, and Interrelation. Am. J. Med. Sci., **203**, 477–489, 1942.

[3] Abels, J. C., Rekers, P. E., Binkley, G. E., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. II. Hepatic Dysfunction. Ann. Int. Med., **16**, 221–240, 1942.

[4] Rekers, P. E., Abels, J. C., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. IV. Fat Metabolism: A Method of Study. J. Clin. Invest., **22**, 243–248, 1943.

[5] Rasmussen, L. H., Abels, J. C., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. XIII. The Utilization of Nitrogen, Especially by Patients with Gastro-Intestinal Cancer. To be published.

CONGENITAL DUODENAL OBSTRUCTION

CARL G. MORLOCK, M.D.
DIVISION OF MEDICINE
AND
HOWARD K. GRAY, M.D.
DIVISION OF SURGERY
MAYO CLINIC
ROCHESTER, MINNESOTA

DUODENAL OBSTRUCTION is a common lesion of adult life and is often seen as a complication of benign duodenal ulcer. Chronic duodenal obstruction which results from a congenital anomaly is rare, particularly among adults. The first case of congenital duodenal obstruction recorded is that reported by Calder,[1] in 1732. Instances of this abnormality were mentioned only infrequently in the literature until the possibility of its occurrence became rather generally recognized. Kellogg[2] stated that congenital occlusion of the intestines was recorded clinically 49 times in 366,000 cases, but that records of postmortem examinations placed its incidence somewhat higher. Kellogg found that in 31 per cent of cases of intestinal occlusion the duodenum is involved. The causes of congenital duodenal obstruction are usually divided into intrinsic and extrinsic causes. Among the intrinsic causative factors are atresia of the lumen, formation of a septum, and complete absence or suppression of segments. Among the extrinsic factors are included abnormal fixation of the duodenum, persistence of the hepaticoduodenocolic ligament, annular pancreas and vascular anomalies. Prenatal mesenteric cysts, tumors or cysts of the liver and pancreas are also known to cause duodenal obstruction. It is common to find associated intra-abdominal anomalies in cases in which congenital duodenal obstruction exists. Malrotation of the intestine frequently results in chronic duodenal obstruction. McIntosh and Donovan,[3] and Wakefield and Mayo,[4] have given excellent reviews of this subject, with a presentation of cases demonstrating this factor as a cause.

Duodenal obstruction secondary to a congenital anomaly is usually manifest soon after birth. If the obstruction is complete, the condition is incompatible with life and unless it is recognized and relieved, death will occur in from one to twelve days. Reports of successful surgical relief of these obstructions in early life are appearing more frequently. With partial obstruction, life may be considerably prolonged and the patient may reach adulthood. It has been stated[5] that regardless of how long the first appearance of symptoms is delayed, these infants do not attain the development of normal children. This statement must be modified by the knowledge that in certain cases of incomplete obstruction normal development may occur. This fact is demonstrated by the case to be reported herein.

The symptoms of congenital occlusion depend largely on the degree of obstruction present. Vomiting always occurs, and is severe and persistent

if the obstruction is complete; it may be intermittent if the obstruction is incomplete. The vomitus may or may not contain bile; it usually contains undigested particles of food and occasionally fresh blood. If, as frequently occurs, enlargement of the duodenum becomes marked, distention involving the upper part of the abdomen, most particularly the right side, and an apparent retraction of the lower part of the abdomen are present. Uncommonly, peristaltic waves are visible and duodenal succussion sounds may be heard. Jaundice has been reported in cases in which the obstruction en-

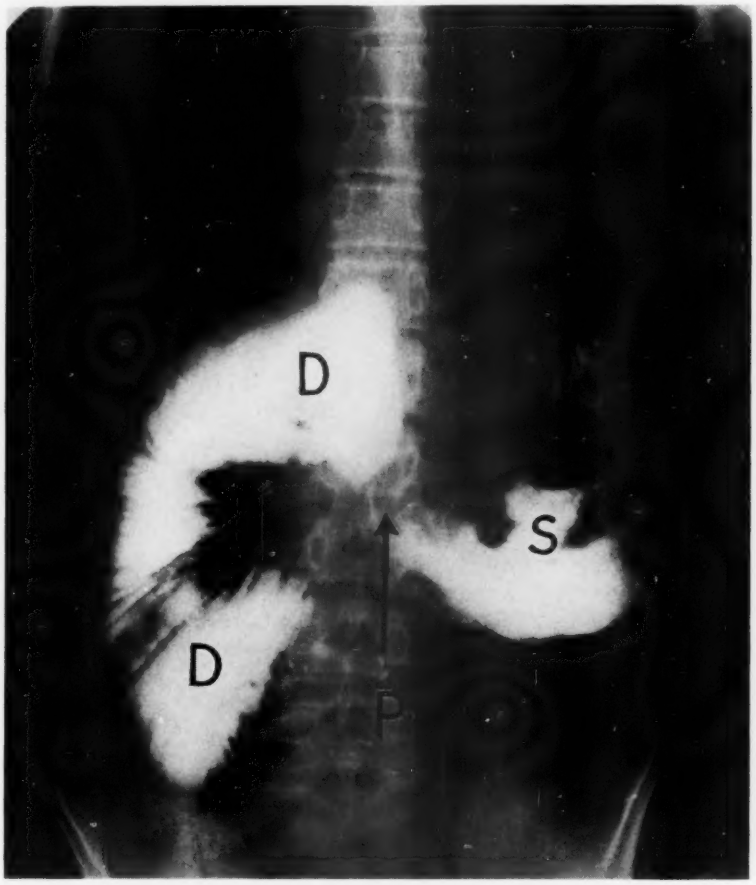


FIG. 1.—Hugely distended duodenum (D). The pyloric canal (P) is widely dilated; the stomach (S) is dilated and atonic.

croaches on the ampulla of Vater. Distress may or may not be experienced. When present, it varies from a dull to a severe colicky pain simulating such abdominal lesions as appendicitis, duodenal ulcer or acute biliary disease. When pain occurs, relief is often afforded by a change in posture or by pressure on the median line below the umbilicus.

A case was recently encountered of congenital duodenal obstruction in

which an extreme degree of duodenal dilatation was attained. Despite the long-standing nature of the condition; the patient, a girl, age 16, did not have her nutrition impaired, and normal development occurred.

Case Report.—A girl, age 16, gave as her chief complaint intermittent attacks of epigastric distention followed by vomiting. Her family history revealed nothing relevant. Her mother had noted that soon after birth the child suffered from frequent attacks of vomiting. She did not attach much significance to this, because long intervals of freedom often followed the episodes of vomiting, and the child developed normally. As the child grew older, it was noted that coarse foods would almost certainly cause an attack of vomiting, whereas freedom from trouble would continue for many weeks if the food ingested was soft and easily assimilated. The material vomited was always stained with bile and the quantity was always large. Often food ingested several days before could be recognized in the vomitus. Pain was not experienced at any time.

The patient's visit to the Mayo Clinic was motivated by an aggravation of symptoms, for the vomiting was becoming of daily occurrence and was preceded by increasing epigastric distention. Despite the aggravation of the symptoms, loss of weight had not occurred and the general state of nutrition was excellent.

The patient was normally developed for her age and did not appear seriously ill. She measured 63 inches (160 cm.) in height and weighed 118 pounds (53.5 Kg.). General physical examination gave normal results except for epigastric fullness and a succussion splash in this region. Peristaltic waves were not visible. Blood pressure 110/70. Urinalysis gave normal findings. The concentration of hemoglobin per 100 cc. of whole blood was 13.5 Gm., the erythrocytes were 4,380,000, and the leukocytes 7,700. The Kline flocculation test for syphillis was negative. The concentration of blood urea and plasma chlorides measured 26 mg. and 561 mg. per 100 cc., respectively. The carbon dioxide combining power was 65 volumes per 100 cc. of plasma. The value for serum proteins was 6.5 Gm. per 100 cc. and the albumin globulin ratio was normal.

A modified Ewald test meal at the end of one hour demonstrated total acidity of 18 units, absence of free hydrochloric acid, and a volume of secretion measuring 1,350 cc. A roentgenogram of the stomach and duodenum (Fig. 1) revealed an obstruction in the lower portion of the duodenum, with tremendous dilatation of the duodenum. The contour of the duodenum was so huge that it exceeded in size that of the stomach. The roentgenogram of the thorax was normal.

The patient was prepared for operation by administration of a liquid diet, repeated gastric and duodenal lavage and the intravenous administration of glucose in physiologic solution of sodium chloride to which small quantities of the synthetic fractions of the vitamin-B complex and ascorbic acid were added. The total daily quantity of fluid aspirated from the stomach before operation varied from 2,300 to 5,100 cc.

Exposure through a primary upper right rectus incision revealed a hugely dilated and markedly thick-walled stomach and duodenum. When the transverse colon was retracted upward, incomplete rotation of the colon and invagination of the duodenum between the leaves of the ascending mesocolon were discovered. The first portion of the jejunum had herniated through an opening in the mesentery of the terminal portion of the ileum. There was marked obstruction of the bowel at this point. Dilatation of the duodenum extended to this point of obstruction; the bowel was normal beyond this point (Fig. 2).

The lateral leaf of the ascending mesocolon was dissected free so that the bowel could be exposed, and the duodenum was dissected free down to the opening in the mesentery of the ileum. The portion of jejunum involved in the herniation was replaced and the opening in the mesentery was closed. This maneuver freed the first portion of the jejunum beyond the obstruction, and it was demonstrated that no intrinsic lesion

FIG. 2.—The appearance of the abdominal viscera at exploration. The second and third portions of the duodenum have invaginated between the leaves of the ascending mesocolon. There is incomplete rotation of the colon. Obstruction of the duodenum has resulted from herniation of first portion of the jejunum through a defect in the mesentery of the ileum. *Inset:* The appearance of the abdominal viscera at the completion of the operation.

existed in this portion of the bowel. A chronically inflamed appendix was removed as an incidental procedure.

Convalescence was uneventful, and when the patient was dismissed from our care, 16 days after the operation, she was free from symptoms in every way. In a communication received from her two months after the operation she stated that her

health was much improved and that she had gained approximately 20 pounds (9.1 Kg.) in the interval.

This case demonstrates that marked duodenal obstruction of congenital origin resulting in severe duodenal deformity need not seriously interfere with normal development. The obstruction in this instance was intermittently partially relieved; this circumstance permitted long intervals of freedom from trouble. The frequency of associated anatomic anomalies in these cases is emphasized. Incomplete rotation of the intestine was probably the fundamental developmental error which brought about the condition noted in this case.

REFERENCES

[1] Calder, James: Quoted by Kellogg, E. L.[2]

[2] Kellogg, E. L.: The Duodenum. P. 300. New York, P. B. Hoeber, Inc., 1933.

[3] McIntosh, R., and Donovan, E. J.: Disturbances of Rotation of the Intestinal Tract: Clinical Picture Based on Observations in 20 Cases. Am. J. Dis. Child., **57,** 116–166, January, 1939.

[4] Wakefield, E. G., and Mayo, C. W.: Intestinal Obstruction Produced by Mesenteric Bands in Association with Failure of Intestinal Rotation. Arch. Surg., **33,** 47–67, July, 1936.

[5] Vail, A. D., and Schwartz, E. J.: Congenital Duodenal Obstruction. J. Missouri M. A., **39,** 12–18, January, 1942.

NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

RAYMOND E. BENSON, M.D.
FELLOW IN SURGERY, MAYO FOUNDATION

CLAUDE F. DIXON, M.D., AND JOHN M. WAUGH, M.D.
DIVISION OF SURGERY, MAYO CLINIC
ROCHESTER, MINNESOTA

DIVERTICULA occur in the jejunum and ileum which are nonmeckelian in origin. Such diverticula are not exceedingly rare. At the Mayo Clinic from 1909 to 1942, inclusive, diverticula of the small intestine, exclusive of duodenal and meckelian diverticula, were observed in 122 cases. Rankin and Martin[11] recorded fifty-two of these cases in 1934. These 52 cases are included in the present report. Approximately 200 cases, aside from the Mayo Clinic cases, are recorded in the literature.

Although these diverticula in the jejunum and ileum are not related to the embryonic omphalomesenteric duct, the work of some investigators[34, 25] has indicated that they may be of congenital origin. Others[11] have presented a variety of evidence to show that these diverticula are, in the great majority of instances, of the acquired type. It is the purpose of this paper to point out the characteristics of these intestinal outpouchings and to discuss the complications to which they may give rise.

Nonmeckelian diverticula of the small intestine occur more frequently in the jejunum than they do in the ileum. Of 122 cases in this series, in 100 the jejunum was affected. In 17 the diverticula were limited to the ileum, and in five the diverticula occurred throughout the small intestine. The proximal portion of the jejunum was most frequently affected.

These diverticula may occur in any position around the circumference of the bowel; however, the majority are situated along the mesentery. Sometimes they are actually within the mesentery, pushing the leaves of this structure apart. The diverticula vary in size from a few millimeters in diameter to large outpouchings. The larger diverticula in this series measured 8 to 9 cm. in diameter. Most of the diverticula seen had an average diameter of 1 to 4 cm. They were, in general, considerably larger than the usual tiny outpouchings seen in the colon (Fig. 1). The openings by which these diverticula communicate with the bowel vary from 1 mm. in diameter to large lumina 3 to 4 cm. in diameter.

When these diverticula are large their walls may be of "tissue paper" thinness. In such cases the wall consists merely of serosa and a very thin layer of mucosa. Small diverticula have thicker walls consisting of the usual intestinal structures.[7] In 44 of the 122 cases only one diverticulum was observed. Thirty-seven of these solitary outpouchings occurred in the jejunum and seven in the ileum. In each of the 12 cases two diverticula were noted, and in the remaining 66 cases, three or more were present. Diverticula in other viscera were observed in 49 of 85 cases in which necropsy

was performed. Of these 49 cases associated diverticula were noted in the colon in 30, in the duodenum in 22, esophageal diverticula in two, and outpouchings of the urinary bladder in ten. In 14 of the cases in which necropsy was performed, there were associated congenital anomalies such as Meckel's diverticulum, malrotation of the intestines, hemangioma of the liver, exstrophy of the urinary bladder and congenital pyloric obstruction.

In the 85 cases of this series in which necropsy was carried out, the diverticula in the small intestine represented the probable primary cause of

FIG. 1.—Postmortem specimen obtained from a white male, age 62; dead of coronary thrombosis, showing multiple large and small diverticula on the mesenteric border of the jejunum.

death in only one instance. Diverticula of the intestines were observed incidentally in all the rest. In 14 cases carcinoma of the stomach, colon, rectum, gallbladder or pancreas was present. In an additional 16, malignant disease occurred elsewhere in the body. Other associated diseases of the gastrointestinal tract and its appendages, observed in the cases in which necropsy was performed, included duodenal and gastric ulcers, cholecystic disease, ulcerative and pseudomembranous colitis, cardiospasm, congenital pyloric obstruction and megacolon.

Nonmeckelian diverticula of the jejunum and ileum are noted in all age-groups (Table I). We have found the reports of only seven cases among children less than ten years of age.[5, 6, 19, 28, 31, 35, 47] The youngest in the present series of patients was 12 years, the oldest 91 years of age. Approximately two-thirds of diverticula of the small intestine (84 of 122 cases) occurred in the male sex.

TABLE I

AGE DISTRIBUTION OF 122 CASES OF NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

Age, in Years	No. of Cases
10–19	2
20–29	7
30–39	6
40–49	15
50–59	24
60–69	38
70–79	23
80–89	5
90+	2

At the Mayo Clinic most of the diverticula of the small intestine have been found at necropsy (85 cases). Some have been recognized during the course of abdominal operations (21 cases). These diverticula are not easily identified at the operating table. Even when they are distended with intestinal contents, they may offer so little resistance to the palpating hand that they will escape identification. Often they are hidden within the leaves of the mesentery.

FIG. 2.—Roentgenogram of small intestine following ingestion of a barium meal, showing multiple large jejunal diverticula. The patient was a female, aged 47, who had had chronic ulcerative colitis for many years.

In 16 of the cases of this series the diverticula were found on roentgenographic examination of the small intestine. According to Weber,[55] if the roentgenologist is given the opportunity, he can diagnose the condition with comparative ease by roentgenoscopic and roentgenographic examination; characteristic roentgenograms (Fig. 2) are produced.

Uncomplicated diverticulosis of the small intestine does not give rise to any characteristic symptoms. In five cases of the group in which necropsy was not performed, all other abdominal organs were ruled out as possible causes of the presenting symptoms by multiple roentgenographic and clinical tests. The patients in these five cases all complained of constipation, flatulence

and abdominal discomfort. The abdominal discomfort varied from mild, indefinite abdominal aching to frequent, moderately severe attacks of pain without definite localization. These symptoms were possibly attributable to the diverticula. Edwards[11] has had a similar experience. He stated that abdominal discomfort and flatulence are the most common symptoms of uncomplicated diverticulosis of the jejunum. These symptoms are in no sense characteristic of any disease and are, therefore, of little aid to the clinician in the diagnosis of this condition.

Diverticula of the small intestines give symptoms when complications occur. Complicating conditions attributable to, or intimately associated with, the presence of diverticula in the jejunum or the ileum were observed in 13 of our 122 cases.

The known complications of, or associated with, diverticula of the jejunum and ileum have been compiled from our cases and those recorded in the literature (Table II). With further experience this list will undoubtedly be found to be incomplete. At present, however, it represents, as far as can be ascertained, a complete summary of the observed pathologic complications of nonmeckelian diverticula of the jejunum and ileum.

TABLE II

COMPLICATIONS OF, OR ASSOCIATED WITH, NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

A. Acute mechanical intestinal obstruction:
   1. From enteroliths formed within diverticula
   2. From pressure of inflammatory mass associated with diverticulitis
   3. From volvulus of the intestine
   4. From stricture or adhesions from ancient diverticulitis
   5. From pressure of filled diverticula on intestine
B. Chronic intestinal obstruction:
   1. Without apparent mechanical obstruction
   2. From stricture or adhesions
C. Inflammatory disturbances varying from mild catarrhal inflammation to gangrene resulting in perforation and peritonitis:
D. Intestinal hemorrhage
E. Rupture of diverticulum:
   1. Spontaneous
   2. Traumatic
F. Foreign bodies:
   1. Bones, etc.
   2. Parasites
   3. Enteroliths
G. Neoplastic disease and formation of heterotopic tissue:
   1. Benign:
      a. Fibroma
      b. Lipoma
      c. Accessory pancreatic tissue
   2. Malignant:
      a. Carcinoma
      b. Sarcoma

Symptoms of chronic intestinal obstruction may be associated with diverticulosis of the small intestine. A remarkable condition is thus produced, and in our cases it was the most commonly observed complication. In this condition the segments of bowel which give origin to the diverticula are markedly dilated and have thick, hypertrophied walls. The changes in the bowel are similar to those found in a loop of intestine which has been ob-

structed mechanically for a long period. In three of the six cases of diverticulosis, with symptoms of chronic obstruction of the jejunum, of this series, however, we did not observe any mechanical obstruction to which could be attributed the dilatation and hypertrophy of the segments of bowel affected by the diverticulosis. This unusual picture of "chronically obstructed-appearing" intestine and diverticulosis of the involved segments without demonstrable mechanical interference with the continuity of the bowel, may represent a "functional" type of obstruction. The following cases are illustrative.

REPORT OF CASES

Case 1.—A male, age 51, entered the clinic complaining of intermittent periods of epigastric distress, flatulence and occasional abdominal distention of 20 years' duration. During the month prior to his admission his symptoms had been severe and had been accompanied by attacks of distressing pain in the left upper quadrant of the abdomen. There had not been any vomiting or obstipation. Roentgenoscopic examination of the small intestine after the patient had ingested a barium meal revealed evidence of chronic obstruction of the small bowel.

Abdominal exploration was performed, and it was found that beginning about 12 or 14 inches (30 or 36 cm.) below the origin of the jejunum were multiple diverticula involving the bowel for a distance of 8 to 10 feet (2.4 to 3.0 meters). These diverticula were all on the mesenteric border of the bowel and protruded between the layers of the mesentery. They varied in size from 2 to 6 or 8 cm. They were literally studded along the mesenteric border of the intestine. Many of the diverticula had a cystic appearance and were thin-walled, almost like tissue paper, as compared with the thickened wall of the bowel itself. In all the large diverticula a distinct opening into the bowel could be felt by invaginating the wall of a diverticulum into the lumen of the bowel. In some, the opening would admit two fingers. The diverticula could be compressed easily, the air which they contained passing readily into the intestine. The jejunum was dilated to two and one-half times its normal size, and the walls were thickened and hypertrophied. A thorough search, however, did not reveal any evidence of mechanical interferences with the continuity of the bowel. The remainder of the intestinal tract, including the stomach and duodenum, was normal. A side-to-side anastomosis was made between the jejunum and the first part of the ileum. The affected portion of the bowel was thus short-circuited. The postoperative course was essentially uneventful.

In the following case the condition was similar to that of Case 1, but more extensive and advanced; the duodenum also being involved in the pathologic process. The extreme difficulties of the radical surgical cure of the condition are well emphasized.

Case 2.—A male, age 45, entered the clinic complaining of having had intermittent, progressively more severe and frequent attacks of nausea, vomiting, cramping upper abdominal pain, borborygmus and looseness of the bowels. He had lost 30 pounds (13.6 Kg.) and was quite weak. On one occasion he had vomited a large quantity of dark blood. Roentgenoscopic examination of the small intestine after the patient had ingested a barium meal showed evidences of obstruction of the duodenum and duodenal diverticulosis.

Abdominal exploration was performed, and many diverticula were found along the mesenteric aspect of the upper five feet (1.5 meters) of jejunum and in the duodenum. Many of these were as large as an "adult's fist" and extremely thin-

walled. The duodenum and upper part of the jejunum were markedly dilated, up to four inches (10 cm.) in diameter, and their walls were thick and hypertrophied. Thorough search, however, did not reveal any mechanical obstruction. The common bile duct emptied into one of the large duodenal diverticula. A short-circuiting procedure was impractical. Resection of the involved portion of the bowel was performed. The common duct was explored, its opening into one of the diverticula ascertained, and its connection with this diverticulum severed close to the ampulla of Vater. The second and third portion of the duodenum and the upper five feet (1.5 meters) of

FIG. 3.—Case 2: Diverticulosis and chronic obstruction of the jejunum. Surgical specimen, 145 cm. in length, consisting of a portion of duodenum and proximal jejunum. The bowel is markedly dilated and hypertrophied. Many thin-walled diverticula are present on the mesenteric border. No mechanically obstructing lesion was observed.

the jejunum were included in the resection. The ends of the duodenum and the jejunum were inverted and antiperistaltic anterior gastrojejunostomy (side-to-side) was performed. The end of the common bile duct was then implanted into the blind end of the jejunum which projected beyond the gastrojejunal stoma. The common bile duct was drained with a T-tube. The operation was difficult because of the friability of the bowel and the tendency of the tissue paper-like walls of the divertic-

ula to rupture after the slightest trauma and contaminate the peritoneum. The patient expired 24 hours after operation. Postmortem examination was not obtained.

A photograph of the pathologic specimen is reproduced in Figure 3. The segment of bowel removed measured 145 cm. in length. The diverticula varied in size from 1 to 8 cm. in diameter.

In the preceding cases extensive mesenteric diverticulosis was considered the cause of the changes in the bowel by interfering in some way with the nerve supply or mechanically with the function of the intestine. The following case, however, demonstrated that the same type of "chronically obstructed-appearing" bowel may be observed when only one diverticulum is present. This would seem to indicate that the disturbance of intestinal function leading to dilatation, hypertrophy and thickening of the intestine is not always explained adequately by the presence of the diverticula. The diverticulosis is probably a phenomenon of secondary importance.

Case 3.—A female, age 63, came to the clinic complaining of progressively more severe constipation of many years' duration. For one year prior to admission constipation had been relieved only by large doses of cathartics, and there were frequent attacks of gaseous abdominal distention and cramping abdominal pain. In the three months immediately preceding admission several episodes of severe abdominal distention and cramps, obstipation and repeated emesis had occurred. Roentgenographic examination of the stomach, small intestine and colon did not reveal any definite evidence of obstruction. The rate of passage of ingested barium through the small intestine was delayed, however, the opaque meal reaching the cecum in 72 hours.

Abdominal exploration was performed. There were many adhesions between the abdominal wall and the hepatic flexure of the colon at the site of a former cholecystectomy. There was no demonstrable mechanical obstruction of any portion of the intestinal tract. A portion of the jejunum was dilated to about three times normal size, and its walls were thick and hypertrophied. This obstructed appearance of the bowel began at the duodenojejunal angle and continued for about two and one-half feet (76 cm.). Distally, the bowel was perfectly normal in appearance. There was one diverticulum, the size of an English walnut, approximately in the middle of the dilated segment of jejunum. No evidence of inflammation about this diverticulum or of mechanical interference with the intestinal lumen by the diverticulum could be found. The adhesions about the gallbladder were separated and the abdomen was closed. The postoperative course was uneventful.

Though the relation of the diverticulum to the intestinal changes is not understood in the foregoing case, the diverticulum must in some way have played an important part in the pathologic changes seen in the bowel. A similar segmental change in the small intestine, consisting of hypertrophy and dilatation without diverticulosis, is practically an unknown condition.[21]

In the following cases mechanical obstruction of the bowel was demonstrable.

Case 4.—A male, age 64, entered the clinic complaining of loss of appetite and of weight. He had had an operation for intestinal obstruction five years prior to admission. He had had anorexia for one year and had lost 20 pounds (9.1 Kg.). During the two weeks immediately preceding his coming to the clinic, he had vomited repeatedly. Roentgenoscopic examination of the small intestine showed evidences of an obstruction lesion in the upper part of the jejunum.

Celiotomy revealed the duodenum and a portion of the adjacent jejunum to be

markedly dilated and to have thickened walls. There were multiple diverticula present in the mesenteric aspect of the dilated portion of jejunum. These varied considerably in size (Fig. 4), the largest being 7 to 8 cm. in diameter. Further exploration revealed multiple adhesions between the loops of jejunum, which were dilated and the site of diverticulosis. Some of these adhesions definitely constricted the intestinal lumen but at no point was there complete intestinal obstruction. The adhesions were freed, the appendix was removed, and the abdomen closed. During the immediate postoperative course there was intestinal obstruction which soon subsided after conservative treatment. After the first postoperative week, convalescence was normal.

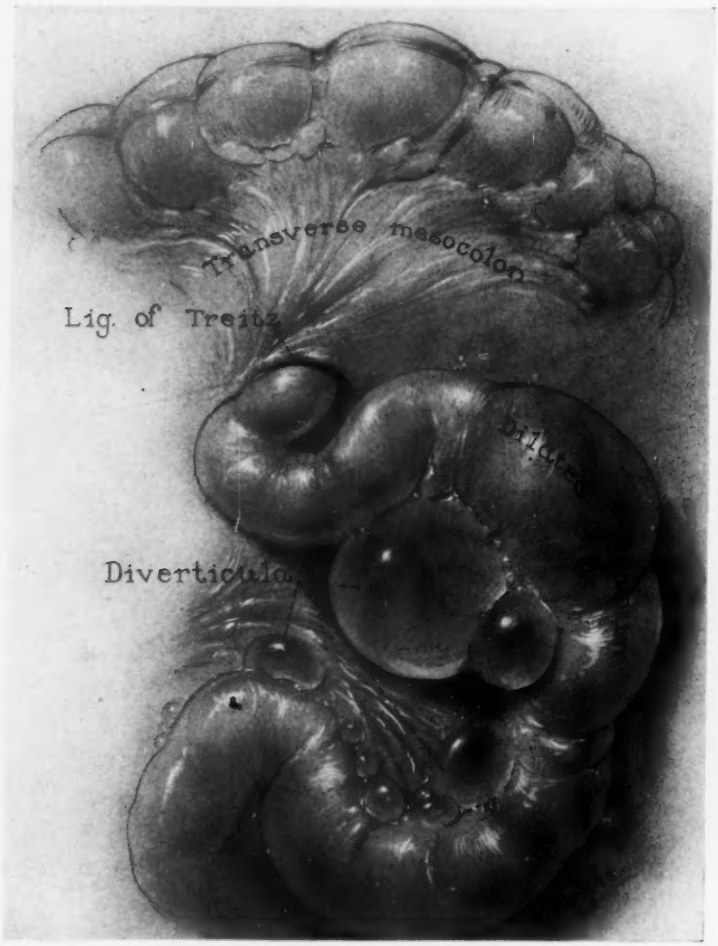


FIG. 4.—Case 4: Diverticulosis and chronic obstruction of the small intestine, showing dilatation and thickening of the intestinal wall. Multiple diverticula are present on the mesenteric aspect. Obstruction resulted from adhesive bands.

Case 5.—A male, age four, entered the clinic with the history and findings of recurrent intestinal obstruction. Celiotomy for intestinal obstruction and adhesions had been performed twice prior to admission. After a period of observation, further surgical treatment for recurring obstruction of the small bowel was advised. The parents decided to try medical management.

Nine years later the patient returned to the clinic, with a history that he had been constantly an invalid because of repeated attacks of intestinal obstruction. His general state of health was very poor. He now accepted surgical treatment.

Celiotomy was performed. The entire intestinal tract was observed to be "firmly bound down by many dense adhesions." The jejunum was dilated and had thickened walls. On the mesenteric aspect of this dilated portion of bowel were many diverticula, some of which were 6 to 7 cm. in diameter. These large diverticula were extremely thin-walled and friable. The adhesions that were kinking and obstructing the small bowel were sectioned as completely as possible, and the abdomen was closed. The patient expired on the nineteenth postoperative day of peritonitis and exhaustion.

Case 6.—A male, age 72, came to the clinic complaining of dyspnea, cough, flatulence, intermittent abdominal distention and constipation. Roentgenologic studies of the stomach and colon gave negative results. Roentgenoscopic examinations of the small intestines revealed extensive diverticulosis. Multiple small and large diverticula were observed in the duodenum and jejunum, the largest being about 6 cm. in diameter. In addition, the jejunum was moderately dilated as though chronically obstructed. No definite obstructing lesion could be visualized. Because of the patient's age, the associated pulmonary disease and the nonemergent character of the abdominal symptoms, operation was not advised.

Spontaneous perforation of a diverticulum of the jejunum or ileum may occur. Several such cases have been recorded in the medical literature.[7, 10, 13, 16, 17, 31, 48, 52] In these there is sudden, severe abdominal pain followed by the signs and symptoms of rapidly spreading peritonitis. Death ensues quickly unless the surgeon intervenes and closes the perforation. The following case is illustrative:

Case 7.—A female, age 57, underwent cholecystectomy and exploratory choledochostomy for subacute cholecystitis supervening on chronic cholecystitis, as well as for cholelithiasis and subacute pancreatitis. The postoperative course was marred by a low-grade febrile reaction for the first seven days but, aside from this, progress was essentially satisfactory until the ninth day. On the ninth postoperative day the patient was seized suddenly with severe abdominal pain. The signs of rapidly spreading peritonitis became evident and death ensued within 48 hours.

At necropsy, diffuse purulent peritonitis was observed. There were five diverticula in the jejunum, each of which measured 2 to 3 cm. in diameter. In four of these outpouchings there was no evidence of pathologic change. The wall of the fifth, however, was necrotic and contained a perforation 5 mm. in diameter. There was, in addition, an abscess of the capsule of the liver. This abscess had ruptured. On microscopic examination of this diverticulum it was observed that the walls were necrotic and infiltrated with inflammatory cells.

Benign tumors of nonmeckelian diverticula of the jejunum and ileum have been recorded very rarely in the literature. Brandes[5] has reported the occurrence of a lipoma in association with a jejunal diverticulum. Other instances in the literature have not been found. Our series contains one fibroma of an ileal diverticulum and, in another case, the formation of heterotopic tissue in a jejunal diverticulum (accessory pancreas).

Case 8.—A male, age 34, died of pulmonary complications after ileostomy had been performed as a first step in the surgical treatment of megacolon. At necropsy, several diverticula were observed on the mesenteric border of the terminal portion

of the ileum. The largest diverticulum was 3 cm. long and 1 cm. in diameter. One of these diverticula was completely filled with a globular mass which measured 4 cm. in diameter. Histologic examination of this tumor revealed it to be a benign fibroma. It had its origin in an ileal diverticulum (Fig. 5).

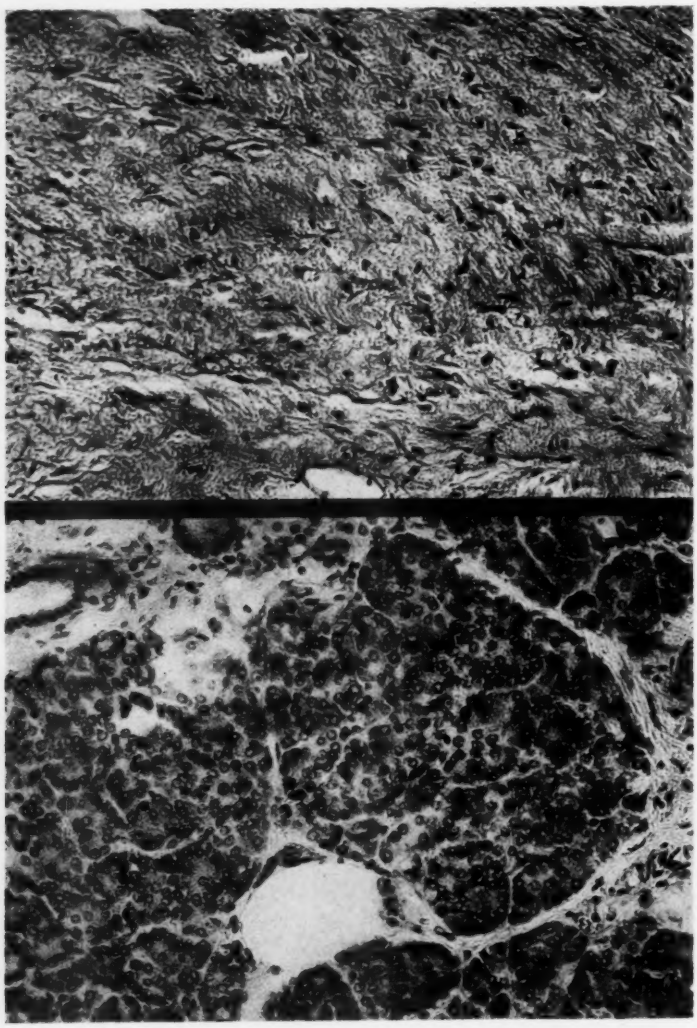


FIG. 5.—Case 8: Fibroma originating in a nonmeckelian ileal diverticulum. (x 175)

FIG. 6.—Case 9: Pancreatic heterotopia. Typical pancreatic tissue found in the tip of a large jejunal diverticulum. (x 175)

Case 9.—A female, age 54, died after total abdominal hysterectomy for carcinoma of the fundus uteri. At necropsy, a solitary diverticulum, measuring 5 by 4 cm., was found on the mesenteric aspect of the upper part of the jejunum. In the tip of this outpouching there was a small, firm tumor. Microscopic examination of this nodule showed it to be composed of typical pancreatic tissue (Fig. 6). The condition was aberrant pancreas in a jejunal diverticulum.

Diverticula of the gastro-intestinal tract, in general, do not show any particular or unusual tendencies to undergo malignant degeneration. In the small intestine both primary carcinoma and diverticula are rare. Morrison and Feldman[36] have recorded an instance of a primary carcinoma in a duodenal diverticulum. Nygaard and Walters,[38] in a thorough review of the literature in 1937, were able to collect six instances of carcinoma and four of carcinoid tumors which had as their primary site a meckelian diverticulum. To the present, however, no undoubted instance of primary carcinoma of a nonmeckelian diverticulum of the jejunum has been recorded. The following protocol, therefore, significantly records such a case:

Case 10.—A male, age 27, came to the clinic complaining of progressively more severe attacks of cramping pain in the lower part of the abdomen associated with anorexia, vomiting and occasional diarrhea. He had lost 20 pounds (9.1 Kg.). A tumor was palpable in the left lower abdominal quadrant. The concentration of hemoglobin was 9.8 Gm. per 100 cc. of blood.

Abdominal exploration revealed an irregularly rounded, tumorous mass, the size of an orange, in the left lower portion of the abdomen. This tumor was intimately attached to the mesenteric wall of the midportion of the jejunum but did not extend into the lumen of the bowel. It was contained in a large, solitary diverticulum of the jejunum. There were a number of enlarged lymph nodes in the omentum and in the mesentery of the involved portion of bowel. There was, however, no palpable evidence of extension of the growth into the liver, pelvis or other regions, nor was there any evidence of a primary malignant lesion elsewhere within the abdomen. Resection of the involved segment of jejunum, along with the tumor, a generous portion of the mesentery and practically all of the omentum was performed. Both ends of the jejunum were closed, and the continuity of the lumen was obtained by a side-to-side anastomosis. The postoperative course was uneventful and 22 months later the patient reported that he was in excellent health.

Photographs of the pathologic specimen are presented in Figure 7. The tumor measured 8 by 8 by 4.5 cm. It had had its origin in a large diverticulum on the mesenteric wall of the jejunum. It completely filled the diverticulum, but had not extended into the wall or lumen of the bowel. Histologic examination proved it to be a small cell adenocarcinoma, Grade 4 (Broders).

In Meckel's diverticula sarcomata are of more frequent occurrence than carcinomata, according to Nygaard and Walters.[38] These authors, in 1937, were able to collect fifteen instances of sarcomata arising in Meckel's diverticula. No case of primary sarcoma of a nonmeckelian diverticulum of the jejunum or ileum has been established as yet, the nearest approach to it being the following case in which a leiomyosarcoma was observed in association with a diverticulum:

Case 11.—A male, age 47, came to the clinic complaining of indefinite abdominal symptoms. After inconclusive examination abdominal exploration was performed. About four inches (10 cm.) distal to the ligament of Treitz a tumor, 2.5 cm. in diameter, was observed on the mesenteric aspect of the jejunum. About six inches (15 cm.) below this, on the mesenteric border, was a jejunal diverticulum about 2.5 cm. in depth. A segmental resection of that portion of the intestine which contained both the diverticulum and the tumor was performed. Histologic examination of the tumor

FIG. 7.—Case 10: Primary carcinoma of a jejunal diverticulum. *a*. Inside view, with jejunum opened along line of attachment of its mesentery, showing opening into diverticulum; *b*, lateral view showing mass of malignant tissue filling the diverticulum; *c*, small cell adenocarcinoma, Grade 4 (Broders) (×80)

showed it to be a leiomyosarcoma, Grade 1 (Broders). This sarcoma had not arisen in a diverticulum.

This case is presented because of the association of the two conditions, jejunal diverticulum and leiomyosarcoma.

COMMENT

Acute mechanical intestinal obstruction is the most commonly reported complication of nonmeckelian diverticula of the jejunum.[3, 4, 6, 9, 12, 14, 16, 18, 20, 23, 27-30, 32, 33, 37, 40, 42, 46, 49, 51, 53, 54, 56] Obstruction of the intestine may result from the formation of enteroliths within diverticula; from pressure of an inflammatory mass associated with diverticulitis; from volvulus of the bowel initiated by diverticula; from stricture or adhesions produced by recent or ancient diverticulitis; or from the pressure of large filled diverticula on the adjacent bowel.

In the case reported by Christ[9] the obstruction was caused by a large mushroom-shaped coprolith, 6 x 4 x 3 cm., which had been displaced from a diverticulum and was unable to pass through the ileum. Enterotomy was performed, and the patient recovered.

Stiven[49] has recorded an instance of volvulus which was caused by the interlocking of a large diverticulum in the terminal ileum, with a diverticulum of similar size which originated from the proximal jejunum. The necks of the two diverticula were twisted, causing a band, over which a loop of small intestine was kinked and obstructed. The volvulus was freed and the patient recovered.

Gordinier and Sampson's[23] case illustrates the intestinal obstruction that may result from diverticulitis. At celiotomy upon a female, age 45, a severely inflamed diverticulum was found, which was producing adhesions and obstruction of the intestine. This diverticulum was excised and a drainage tube inserted. The patient recovered.

Diverticulitis does not always produce intestinal obstruction, however. Inflammatory disturbances of jejunal and ileal diverticula may vary from mild catarrhal inflammation to gangrene, producing perforation and peritonitis. In the cases of our series in which necropsy was performed, there were two instances in which mild catarrhal inflammation of jejunal diverticula was observed on routine examination. If the diverticulitis gave any symptoms in these two cases they were overshadowed completely by the more serious disturbances which led to fatal terminations. It seems likely, however, that such mild inflammations of diverticula might give rise in otherwise healthy persons to signs and symptoms of an inflammatory intra-abdominal disease. Only severe diverticulitis will produce symptoms and signs urgent enough to warrant abdominal exploration. The literature contains several such reports.[2, 7, 11, 15, 22, 23, 44, 56]

It is surprising, in view of the thinness of the walls of many of these diverticula of the jejunum and ileum, that rupture does not occur more

often than is observed. Only a few cases have been recorded in the literature.[1, 8, 45] The report of Butler and Weeden[8] is illustrative. A male, who had always been previously well, was kicked in the abdomen by a horse. Urgent signs of a serious intra-abdominal disturbance made their appearance immediately, and celiotomy was performed. At operation, a ruptured intramesenteric diverticulum was found and closed. The patient died ten hours after the operation. At autopsy, an additional ruptured diverticulum which had escaped observation at operation was found.

Hemorrhage may occur from nonmeckelian diverticulum of the jejunum and ileum.[24, 26, 47, 50] The loss of blood thus sustained may be so severe as to demand appropriate intervention.[24]

Foreign bodies may become lodged in the diverticula. Examples of retained ingested bones,[39] food particles,[52] enteroliths,[9, 42, 51, 54, 57] and parasites[22, 43] have all been reported.

Uncomplicated and asymptomatic diverticulosis of the jejunum or ileum does not require surgical treatment. In evaluation of symptoms of diverticulosis, all other possible causes of the complaints must be ruled out, for, as we have pointed out, the outpouchings are usually silent, and the patient's distress may be due to an unsuspected disease of the gallbladder, stomach or colon. To date, no patient upon whom the diagnosis of uncomplicated diverticula of the jejunum or ileum has been made, has been operated upon at the clinic for the relief of the condition.

When acute complications, such as intestinal obstruction, diverticulitis or rupture of a diverticulum, present themselves, surgical treatment is often imperative. In operations upon such cases it is probably best to limit surgical treatment to relief of the urgent condition.

An attempt at surgical elimination of the diverticula is justified when persistent distressing symptoms; the syndrome of diverticulosis and chronic obstruction; or other chronic complications are present. As a rule, enteroenterostomy, side-tracking the involved segment, is preferable to resection, and anastomosis in one stage unless the diverticula are localized to a small segment. These patients are often poor surgical risks. There is also a distinct danger of rupturing one of the fragile, thin-walled diverticula during an extensive operative procedure. A short-circuiting procedure alone may relieve the patient of his symptoms. If not, the involved segment may be resected with less risk at a later date.

SUMMARY

One hundred twenty-two cases of nonmeckelian diverticula of the jejunum and ileum are reviewed. The anatomic and clinical characteristics of these diverticula have been presented. A complete list of the observed pathologic conditions to which such diverticula may give rise is presented. The syndrome of diverticulosis and chronic obstruction of the small intestine is described, but is not considered to be characteristic. The first reported case of primary

carcinoma of a jejunal diverticulum is contained herein, along with several other unique and interesting complications of nonmeckelian diverticula of the jejunum and ileum.

REFERENCES

1. Adams-Ray, Jack: A Unique Case of Subcutaneous Abdominal Injury, with Intramesenterial Rupture of Diverticulum of the Small Intestine and Subsequent Peritonitis. Acta chir. Scandinav., **81,** 398–404, 1938.
2. Beigler, S. K., Bloom, A. R., and Wruble, Joseph: Diverticulum of the Jejunum. Am. J. Surg., **17,** 109–110, July, 1932.
3. Boling, J. R.: Multiple Diverticula of Small Intestine. J. A. M. A., **95,** 267, July 26, 1930.
4. Boling, J. R.: Multiple Diverticula of Jejunum, with Resection. J. A. M. A., **96,** 526–527, February 14, 1931.
5. Brandes, Karl: Über Dünndarmdivertikel; nebst einem Beitrag zur Beobachtung eines hochsitzenden Dünndarmdivertikels bei einem Darmlipom. Deutsche Ztschr. f. Chir., **215,** 390–402, April, 1929.
6. Buchwald, Alfred, and Janicke, Otto: II. Über Darmcysten (Enterokystome) als Ursache eines completen Darmverschlussels. Deutsche med. Wchnschr., **13,** 868–869, October 6, 1887.
7. Butler, R. W.: Observations upon Multiple Intramesenteric Diverticula of the Small Intestine. Brit. J. Surg., **21,** 329–346, October, 1933.
8. Butler, R. W.: Traumatic Rupture of Intramesenteric Diverticulum of the Jejunum. Brit. J. Surg., **25,** 277–279, October, 1937.
9. Christ, Andreas: Multiple Divertikel des Jejunum; Anatomische und klinische Beiträge zur Kenntnis eines seltenen Krankheitsbildes. Deutsche Ztschr. f. Chir., **236,** 560–570, July 9, 1932.
10. Christie, G. W.: Acute Inflammation of a Large Diverticulum of the Jejunum, with Perforation. Brit. M. J., **1,** 990–991, June 24, 1922.
11. Edwards, H. D.: Diverticula and Diverticulitis of the Intestine: Their Pathology, Diagnosis and Treatment. Baltimore, Williams & Wilkins, 1939, 335 pp.
12. Finney, J. M. T., Jr.: Discussion. Annals of Surgery, **107,** 798–799, May, 1938.
13. Flynn, Richard: A Case of Ruptured Jejunal Diverticulum. Australian & New Zealand J. Surg., **3,** 192–194, October, 1933.
14. Fort, F. T.: Diverticulum of the Small Intestine. Kentucky M. J., **19,** 208, April, 1921.
15. Fort, F. T.: Solitary Jejunal Diverticulum of Long Duration; complete intestinal obstruction; operation; recovery. Tr. South. S. A., **41,** 292–295, 1928.
16. Fraser, Ian: The Diverticula of the Jejuno-ileum. Brit. J. Surg., **21,** 183–211, October, 1933.
17. Gerster, J. C. A.: Diverticula of Jejunum. Annals of Surgery, **107,** 783–800, May, 1938.
18. Gladtke, M.: Dünndarmdivertikel. Deutsche Ztschr. f. Chir., **224,** 345–347, 1930.
19. Glans, Alfred: Zur lehre der kongenitalen Darmdivertikel. Schweiz. med. Wchnschr., **50,** 1024–1025, November 4, 1920.
20. Godard, H., Bourdial and Zourekatis: Un cas de diverticulose jéjuno-iléale. Ann. d'anat. path., **9,** 311–315, March, 1932.
21. Goinard, E., Goinard, P. E., and Chevaux: Présentation d'une diverticulose de jéjunum. Presse méd., **1,** 298, March 7, 1928.
22. Goinard, Pierre, and Courrier, R.: Sur la constation de parasites dans des diverticules multiples du jejunum. Ann. d'anat. path., **6,** 189–196, February, 1929.
23. Gordinier, H. C., and Sampson, J. A.: Diverticulitis (not Meckel's) causing Intestinal Obstruction. J. A. M. A., **46,** 1585–1590, May 26, 1906.

[24] Guthrie, Donald, and Hughes, F. A., Jr.: Diverticulosis of the Small Intestine: Report of Three Cases. Surgery, **1**, 595–609, April, 1937.
[25] Guthrie, R., and Wakefield, E. G.: Unpublished data.
[26] Haltung: Quoted by Rankin, F. W., and Martin, W. J., Jr.[40]
[27] Hubeny, M. J., and Pollack, Simon: Diverticulosis of the Small Intestine: Report of a Case with Intestinal Obstruction. Am. J. Roentgenol., **40**, 689–694, November, 1938.
[28] Hunter, J. I.: A Mesenteric Cyst of Jejunal Origin complicated by Retrojejunal Position of the Transverse Colon. Brit. M. J., **2**, 800–802, October 28, 1922.
[29] Johns, F. S.: Diverticula of Jejunum: With Case Report. South. Med. & Surg., **99**, 26–167, June, 1937.
[30] Kaspar, Fritz: Der Divertikelileus. Arch. f. klin. Chir., **141**, 389–418, 1926.
[31] Kozinn, P. J., and Jennings, K. G.: Jejunal Diverticulitis: Its Occurrence in a Two-year-old Girl. Am. J. Dis. Child., **62**, 620–623, September, 1941.
[32] Lambret, O., and Surmont, I.: Un cas de diverticules multiples du jéjuno-iléon. Arch. d. mal. de l'app. digestif., **18**, 765–771, June, 1928.
[33] Larson, E. M.: Multiple Diverticula of the Jejunum. West. J. Surg., **46**, 127–131, March, 1938.
[34] Lewis, F. J., and Thyng, F. W.: The Regular Occurrence of Intestinal Diverticula in Embryos of the Pig, Rabbit and Man. Am. J. Anat., **7**, 505–520, 1908.
[35] McMurrich, J. P., and Tisdall, F. F.: A Remarkable Ileal Diverticulum. Anat. Rec., **39**, 325–332, August, 1928.
[36] Morrison, T. H., and Feldman, Maurice: Autopsy Report of a Case of Primary Carcinoma in a Duodenal Diverticulum. Ann. Clin. Med., **5**, 326–329, October, 1926.
[37] Neumann, A.: Wiederholter Ileus wegen eigenavtiger Dünndarm-affektion. Deutsche Ztschr. f. Chir., **126**, 185–192, December, 1913.
[38] Nygaard, K. K., and Walters, Waltman: Malignant Tumors of Meckel's Diverticulum: Report of a Case of Leiomyosarcoma. Arch. Surg., **35**, 1159–1172, December, 1937.
[39] Ogloblina, S.: Multiple Divertikel des Dünndarms. Zentralbl. f. Chir., **58**, 3169, December 12, 1931.
[40] Pinninger and Burman: Quoted by Rankin, F. W., and Martin, W. J., Jr.[41]
[41] Rankin, F. W., and Martin, W. J., Jr.: Diverticula of the Small Bowel. ANNALS OF SURGERY, **100**, 1123–1135, December, 1934.
[42] Renaud, Maurice, and Bergeret: Deux diverticules de l'intestin. Bull. Soc. anat. de Paris, **91**, 220–223, April, 1921.
[43] Rosedale, R. S.: Jejunal Diverticulosis. Surg., Gynec. & Obst., **61**, 223–228, August, 1935.
[44] Rosedale, R. S., and Lawrence, H. P.: Jejunal Diverticulosis. Am. J. Surg., **34**, 369–373, November, 1936.
[45] Schunk, P. M.: Traumatic Rupture of a Jejunal Diverticulum. Rocky Mountain M. J., **36**, 327–328, May, 1939.
[46] Simons, E. J.: Multiple Diverticula of Small Intestine: Report of Case. Minnesota Med., **11**, 752–753, November, 1928.
[47] Somerford, Anne E.: Two Cases of Intestinal Disease in Infancy. Lancet, **1**, 1015, May 10, 1930.
[48] Spackman, J. G.: Perforation of a Jejunal Diverticulum. ANNALS OF SURGERY, **84**, 778–780, November, 1926.
[49] Stiven, H. E. S.: Jejuno-ileal Diverticulitis. Lancet, **2**, 704–705, September 29, 1934.
[50] Tengwall, Ernst: Case of Multiple Diverticula in the Jejunum. Acta chir. Scandinav., **68**, 162–170, 1931.
[51] Terry, W. I., and Mugler, F. R.: Diverticula of the Jejunum. Arch. Surg., **2**, 347–353, March, 1921.

[52] Treves, F.: Intestinal Obstruction: Its Varieties, with their Pathology, Diagnosis and Treatment. New York, William Wood & Co., 1900, 565 pp.

[53] Turner, Philip: A Case of Multiple Diverticula of Jejunum. Guy's Hosp. Rep., **89**, 32–46, 1939.

[54] Watson, C. M.: Diverticula of Jejunum: A Case with Enterolith causing Intestinal Obstruction. Surg., Gynec. & Obst., **38**, 67–71, January, 1924.

[55] Weber, H. M.: Roentgenologic Manifestations of Nonneoplastic Lesions of the Small Intestines. J. A. M. A., **113**, 1541–1546, October 21, 1939.

[56] Zagami, Antonio: Sulla mesenterite retrattile; uncaso da diverticolo infiammato del digiuno. Policlinico, **44**, 550–557, October, 1937.

[57] Zengerle: Quoted by Kaspar, Fritz.[30]

Case Report.—A two-year-old female infant was brought to the DeCourcy Clinic in an acutely ill state. She was emaciated, apparently from malnutrition. Her history revealed that the child had been vomiting intermittently over a period of several months. This symptom had become more frequent within the last two weeks. On examination, she was underweight and undernourished. Her tongue had a furred appearance. There was an odor of acetone on her breath. Pulse was rapid, temperature subnormal. She was sent to the Good Samaritan Hospital, where glucose was administered intravenously upon admission, and several blood transfusions were performed.

She responded well to this treatment and, after 24 hours, was able to retain food. Within a week she had gained two pounds. Consequently, we were inclined, at that time, to attribute her vomiting to the acidosis.

Physical Examination.—Palpation of the abdomen revealed a hard nodular mass about the size of a small orange. Two-thirds of the tumor was felt above and one-third below the umbilicus, at the midline. It was freely movable and not particularly tender to touch. Roentgenograms of the stomach and colon, after barium enema, localized the mass as posterior to these structures, in all probability in the lesser peritoneal cavity. This was as definite a roentgenologic diagnosis as could be made.

As the child continued to improve clinically, it was decided to delay surgery until her weight and blood chemistry had reached normal levels. After several weeks, when her general condition was deemed sufficiently good for surgery, operation was performed.

Operation.—Under open ether anesthesia, a right rectus incision was made just external to the midline. Upon incision of the gastrocolic omentum, a hard tumor mass was discovered embedded in the pancreas at the middle portion. The mass was removed with ease. Contrary to our expectation, bleeding was scant. There was, however, some oozing which could not be controlled with hot moist pads.

Our problem was what to do for the large denuded area of pancreas remaining. After some thought, an opening was made in the transverse mesocolon and a large strip of omentum was brought through and sutured to the raw surface in the pancreas with No. 00 catgut. A small rubber tube was inserted below this and brought out through the slit in the gastrocolic omentum. Upon completion of the operation, a small blood transfusion was given.

There was a slight amount of drainage from the tube. It was possible, however, to remove the tube on the eleventh postoperative day. The child improved, and convalescence was smooth and uneventful.

Pathologic Examination.—Gross: Upon opening the tumor, it was found to be a cyst wall containing all the elements comprising a dermoid cyst.

SUMMARY

(1) To date, only two cases of dermoid cyst of the pancreas have been reported.

(2) An additional instance of dermoid cyst of the pancreas occurring in an infant two years of age is described.

(3) Obscurity of symptoms and difficulty of diagnosis are again emphasized.

(4) Satisfactory surgical procedure and treatment are described.

REFERENCES

[1] Judd, E. S.: Cysts of the Pancreas. Minnesota Med., **4**, 75, 1921.

[2] Masson, J. C., and Caylor, H. D.: Dermoid Cyst of the Pancreas. S. Clin. North America, **9**, 837, 1929.

[3] Dennis, W. A.: Dermoid Cyst of the Pancreas. S. Clin. North America, **3**, 1919, 1923.

SPONTANEOUS RUPTURE OF LIVER COMPLICATING PREGNANCY

LEE RADEMAKER, M.D.

SALISBURY, MD.

SPONTANEOUS RUPTURE OF THE LIVER resulting from insignificant or no trauma has been noted in the literature for more than a century. The first known case was reported by Vesalius at some undetermined date. Andral, in 1829, sketchily reported two cases complicating lesions which may have been gummata or carcinomata. In many of the earliest cases there is some possibility that gastric hemorrhage, secondary to liver disease, may have been mistaken for actual rupture of the liver. Thus, a case quoted in Paris Medical, in 1847, by Fauconneau and Dufresne, as reported by Latour, was undoubtedly such an instance.

Abercrombie, as communicated by James Copeland, reported a case of ruptured liver complicating pregnancy in 1844. In this delightfully naive and meticulously detailed report, Abercrombie described a 35-year-old woman who, to obtain relief from "gastrodynia," took recourse to placing a silk handkerchief around her body and pulling it tight to give her relief. On this occasion a servant pulled the handkerchief so tightly that "it made me fear some injury under existing circumstances." Labor followed and normal delivery occurred, followed by collapse some 50 minutes later. The crude stimulants of the time were administered, several famous physicians and surgeons were called in consultation, but the patient died 26 hours after delivery. Autopsy revealed about two pounds of blood in the abdomen and two lacerated openings in the liver substance, about an inch apart. The liver itself presented a mottled appearance throughout and was unusually soft. Bleeding came from a torn branch of the "vena portae."

Devic and Beriel, in 1906, reviewed the literature of spontaneous rupture of the liver. McEwan and McEwan, and Corriden have added more recent and excellent reviews.

Spontaneous rupture of the liver is rare and exceptional. A number of causes for its occurrence have been described. Traumatic rupture we know to be no rarity. Allessandri (1927) stated: "Very exceptionally lesions of the liver are observed as the result of violent muscular exertion, as in the course of parturition or epileptic seizures. In such cases it is usually necessary to assume a diminished resistance of the organ as a necessary condition." Our case, although complicating pregnancy, was not in labor.

Causes other than violent muscular effort are multiple (Table I). From this table it can easily be seen that some associated disease or even minor trauma was present in all but three cases of 28 collected. It is no wonder that Sciacca came to the conclusion that when rupture of the liver occurs with minimal cause, the parenchyma is probably not normal.

TABLE I

CAUSES OF RUPTURE OF THE LIVER OTHER THAN VIOLENT MUSCULAR EFFORT

Date	Author	Age	Cases	Operation	Cause	Result
1829	Andral		2	Autopsy	Carcinoma or gumma	Died
1831	Honore		1	Autopsy	Multiple cavities	Died
1836	Gerard	52	1	Autopsy	None	Died
1844	Sacquepec	44	1	Autopsy	Syphilis	Died
1847	Fauconneau and Dufresne		1	Autopsy	Typhoid fever	Died
1849	Abercrombir	35	1	Autopsy	Pregnancy	Died
1864	Heinzelman		2	Autopsy	Tuberculous peritonitis	Died
1884	Chiari	40	1	Autopsy	Cancer (stomach)	Died
1886	Heinzelman	18	1	Autopsy	Pneumonia	Died
1890	Laurencon	16	1	Autopsy	Syphilis	Died
1892	Pauly	47	1	Autopsy	Biliary colic	Died
1892	Poljakoff		1	Autopsy	Epilepsy	Died
1898	Bar and Keim	Newborn	2	Autopsy	Newborn syphilitic	Died
1899	Carnabel	26	1	Autopsy	Osteotis	Died
1902	Bernard	62	1	Autopsy	Hemoplegia	Died
1905	Nauwerck		1	Unknown	Common duct stone	Unknown
1906	Devic and Beriel	41	1	Autopsy	Syphilis	Died
1921	Walz		1	Autopsy	Aneurysms	Died
1932	Richon and Cachin	34	1	Operation	Exercise and cough	Recovered
1933	Mast and Streamer		1	Autopsy	Pneumonia and primary carcinoma of liver	Died
1934	Robin	28	1	Operation	Trauma	Recovered
1936	Bradley and Garrett	3	1	Operation	None	Recovered
1937	Sciacca		1	Autopsy	Toxic infection	Died
1938	McEwan	8	1	Operation	Malaria	Died
1940	Corriden	9	1	Operation	Slight trauma	Recovered

Recovery from spontaneous rupture of the liver is rare. First of all, only five cases were diagnosed before death, and while four of these recovered with operation, yet only four recovered of 28 reported cases, all within recent years. More accurate diagnosis; more rapid recognition of the acute surgical emergency present; and more adequate means to replace the blood lost, either by transfusions or by autotransfusion (which is not to be recommended due to the possible contamination and sepsis of liver blood), account for the relatively low operative mortality in the five operative cases. Mortality of traumatic rupture varies from 45 to 78 per cent by comparison. Prompt recognition and early operation with adequate blood replacement are obviously the factors most concerned in recovery.

Pathology of rupture of the liver varies with the accompanying lesion of the liver. Thus, a gumma or carcinoma may easily erode into a blood vessel causing a discharge of blood into the liver parenchyma. Again an aneurysm or hemangioma may rupture and bring about a similar result. A vessel may rupture by reason of arteriosclerosis, as was possibly the case in Bernard's patient. A vessel may become occluded with resultant infarct—then ruptured vessels, as Mazel has suggested. In our case, the rapidly rising blood pressure, with toxemia of pregnancy, caused rupture of a blood vessel.

Devic and Beriel and, later, Mazel have formulated this theory of the pathology of spontaneous rupture of the liver: "In traumatic rupture, the rupture is the cause of hemorrhage. In spontaneous rupture, the hemorrhage is the cause of rupture. The chain of events leading to the rupture are infarct, hypervascularization at the periphery, rupture of a vessel, intra-

hepatic hemorrhage, with resulting rupture of the tissue and production of a subcapsular hematoma which, when rupturing the capsule permits escape of blood into the peritoneum leading to peritonitis and death."

Ruptured liver in the newborn presents a different problem than that with which we are concerned. Its literature, theories and occurrency have been thoroughly reviewed in an article by Silver, in 1938.

We have thus been able to collect but 20 cases (the case of Vesalius included) of true spontaneous rupture of the liver. One of these complicated pregnancy, five came to operation, and four recovered. Only one other case could be theoretically associated with high blood pressure as a possible apoplexy—the case of Bernard.

Case Report.—R. H., white, female, age 32, was admitted to the Peninsula General Hospital, referred by Dr. Harry S. Kuhlman of Sharptown, Md. The patient was in the early 8th month of her pregnancy. There had been no abnormality in the pregnancy until two weeks before admission, when Doctor Kuhlman found her blood pressure increased to 160/110, and first found some albumin in her urine. He sent her home to stay in bed, and placed her on a very strict diet, limiting proteins, salt and fluid intake. Despite this care her blood pressure continued to rise, until, on the afternoon previous to admission, it had reached the alarming level of 260/160. Her physician advised hospital care that afternoon. At 6 P.M. she vomited once, and was transferred to the hospital. No labor pains had occurred.

When next seen by Doctor Kuhlman at the hospital, she was in obvious collapse. Blood pressure 60/0; pulse faintly discernible at 160. She stated that she had some dull ache in the right, upper quadrant soon after vomiting but no sharp pain anywhere. Labor had not commenced. No fetal movement had been felt since the attack of vomiting. There was no history of trauma of any kind. A surgical consultation was immediately requested and she was seen by the author a few minutes later.

Physical Examination.—The patient was obviously in severe shock; pallid with grey lips; quiet but very nervous; air hunger and feebly preceptible pulse and blood pressure as above described. Fetal heart sounds were absent. *Clinical Diagnosis:* Ruptured uterus.

Operation.—May 10, 1942: Dr. L. A. Rademaker, and Dr. Robert Starr. Under cyclopropane anesthesia, the abdomen was entered through a lower, midline incision. An incision was made in the lower portion of the uterus and the fetus delivered. There seemed to be an opening in the uterus, and, therefore, a Porro excision of the uterus, tubes and ovaries was done at the supravaginal level. The ligaments and blood vessels were satured. It then became obvious that excessive hemorrhage was still occurring from some place in the upper abdomen and the tear and damage of the liver were found. Two long packs were placed in the damaged portion of the liver, protected by tissue drain in the intra-abdominal part. The patient at this time was in desperate condition and a blood transfusion was administered. The ligaments were tied to the cervical stump but because of the patient's condition no attempt was made to peritonealize. Then the wound was quickly closed in layers about the drains, using chromic catgut in the peritoneum and muscle, stainless steel wire in the fascia, plain catgut in the fat and clips in the skin. The patient left the operating room in poor condition.

Surgical Pathology.—The uterus contained a small, immature dead female fetus. The abdomen was filled with blood. There were multiple fibroid tumors of the uterus itself. The right lobe of the liver contained a vertical tear six inches in length, with an area of degenerated tissue which appeared to be mush, and about the size of a grapefruit.

Postoperative Course.—The patient had a very stormy convalescence; blood transfusions were given on May, 11th, 12th and 13th. Synkamin, blood plasma and glucose were added. Due to pressure of the pack against the diaphragm she developed a pleural effusion, and 600 cc. of bloody, serous fluid were removed by aspiration on May 25, 1942, and repeated daily until May 29, 1942, when but 40 cc. could be obtained.

The pack was removed May 19, 1942, under gas anesthesia in bed, and was followed by a profuse drainage of material so closely resembling blood that the resident became alarmed and repacked the incision. This pack was removed May 24, 1942, and was followed by further drainage of serous bloody material which smelled like biliary drainage but did not appear bile-stained. An abscess of the left breast further complicated recovery—necessitating incision and drainage, under local anesthesia, on June 5, 1942.

Each of these complications produced its storm in temperature, pulse and respiration. Sulfanilamide preparations did much to abate each storm as it occurred. At times the patient's condition seemed entirely hopeless, but she gradually improved after the last complication was conquered, and was discharged July 4, 1942, 57 days since admission. Her chest was clear; the breast had completely healed, her abdominal wound was still draining slightly. Her blood count on June 1, 1942 showed Hb. 66; R.B.C. 3,510,000; W.B.C. 12,250. Her blood pressure on discharge was 165/100, and the urine showed a slight trace of albumin, with specific gravity of 1.011.

Follow-Up.—August 10, 1942: The patient appeared to be quite healthy, with a well-healed solid abdominal scar. She was taking stilbestrol, 0.1 mg. per day, which controlled her hot flushes very well. She was able to work and felt as strong as ever. Her blood pressure was 145/90.

This, as far as we can discover, is the fifth reported case of recovery from a spontaneous rupture of the liver, and the second case of spontaneous rupture of the liver complicating pregnancy. The high blood pressure occurring in a short period of time suggest the cause for apoplexy—especially when a vomiting attack immediately preceded collapse.

Several significant facts appeared:

(1) Careful observation by the family physician made it possible to operate; otherwise, the patient would have died within a few hours, and the diagnosis, if made at all, would have been made at autopsy, as in the majority of reported cases of spontaneous rupture of the liver.

(2) The Porro procedure was the quickest means of removal of the fetus and the uterus to prevent any further bleeding from that source.

(3) Death of fetus as result of hemorrhage of the mother.

(4) Pleural effusion from pressure of the pack on diaphragm.

(5) Prompt multiple blood and plasma transfusions are necessary to save these desperately ill patients.

One is led to speculate if some of those cases of death by collapse during treatment for eclampsia may not be due to undiagnosed rupture of the liver.

SUMMARY

We have reviewed the literature of spontaneous rupture of the liver, finding but four other cases of recovery, and but one other report complicating pregnancy. We have reported such a case of spontaneous rupture of the liver complicating pregnancy and following a rapidly developed hypertension.

This case was operated upon while in desperate condition, under a mistaken diagnosis as to source of hemorrhage. The diagnosis of internal hemorrhage was made early enough so that recovery could occur with the modern methods to combat shock and hemorrhage. Recovery was complicated by pleural effusion, secondary hemorrhage, breast abscess, but final complete recovery ensued.

REFERENCES

1 Abercrombie, James: Hemorrhage of the Liver. London M. Gaz., **34,** 792–795, September 13, 1844.

2 Allessandri, Roberto: Surgery of the Liver. In Nelson's New Looseleaf Surgery. Vol. V, p. 535, 1927.

3 Allen, Arthur W.: Internal Injuries Without Penetrating Wounds. New England J. Med., **205,** 34, 1931.

4 Bernard, Leon: Hemorrhagie Cerebrale Droite. Hemorrhagie hepatique: Mort par inondation sanguine peritoneale. Autopsie, Bull. de la Soe. Anat., **77,** 927, 1902.

5 Bradley, C. E., and Garret, D. L.: Spontaneous Rupture of the Liver in a Child, with Complete Recovery. J. Pediat., **9,** 776, 1936.

6 Carnabel: Rupture spontanee du foie. Bull. et men. Soc. de chir. de Buearest, **2,** 110, 1899.

7 Corriden, Thomas F.: Subcapsular Rupture of the Liver in a Child. Surgery, **8,** 446, September, 1940.

8 Devic, E., and Beriel, L.: L'epoplexie hepatique dans la syphilis: Considerations sur les ruptures spontanees du foie. Ann. de dermat. et syph., **7,** 642, 1906.

9 Filatov, A.: Klinische und experimentelle Beitrage zue Reinfusion des in die Korperhohlen ergossenen Blutes. Arch. d. klin. Chir., **151,** 185, 1928.

10 Genell, Sune: Leberruptur bei Neugeborenen nach Spontangeburt. Act Obst. et Gynee. Scandinav., **9,** 180, 1930.

11 Hedren: Ruptur der Leber und Milz Neugeborener, besonders bei spontaner Geburt, Veirtelj. Schr. f. gericht. Med. U. offentl. San-wesen. 54–230, 1907; Dodane Skador av Bukorganen hos nyfodda, sarskilt fran rattsmedicinsk synpukt (mit vollstandigem Verzeichnis fruherer Literatur), Svenska Lak. Sallsk. handl., **44,** 1, 1918.

12 Heinzellmann, H.: Ein seltener Fall von todtlicher Leberruptur. Dissert. Munchen., 1886.

13 Lamb, Charles A.: Rupture of the Liver. New England J. Med., **221,** 855, 1930.

14 Lewis, Dean, and Trimble, I. Ridgeway: Subcutaneous Injuries of the Abdomen. Annals of Surgery, **98,** 685, 1933.

15 McEwan, John S., and McEwan, Duncan: Spontaneous Rupture of the Liver in Malaria. Annals of Surgery, **107,** 473, 1938.

16 Marchstadt, K. O.: Uber Geplatzte Hemangiome der Leber. Deutsche Ztschr. f. Chir., **250,** 37, 1938.

17 Mast, William H., and Streamer, Charles W.: Primary Carcinoma of the Liver with Spontaneous Rupture. J. A. M. A., **100,** 1684, 1933.

18 Neuwerck: Ruptur der Leber durch Gallenstauung (mit Dermonstration). Munchen. med. Wehnschr., **52,** 931, 1905.

19 Mazel, M.: Aupropos des ruptures spontanees de doie. Rev. de med. legale, **20,** 238, 1914.

20 Pichon, Roger, and Cachin, Marcel: Rupture grave due doie apres traumatisme insignificant. Ann. de med. legale, **12,** 615, 1932.

21 Robin, I. G.: A Case of Ruptured Liver due to Trivial Violence. Guy's Hosp. Rep., **84,** 100, 1934.

[22] Sciacca, Ferdinando: Le rotture quasi spontanee del fegator. Polichinico (sez. chir.), **44**, 254, 1937.

[23] Silver, Harry B.: Rupture of the Liver in the Newborn Infant. J. Pediat., **13**, 542, 1938.

[24] Springer, C.: Reinfusion des asu gedeckten Leber—und Milz-rupturen in die Bauchhole ergossenen Blutes. Med. Klin., **34**, 647, 1938.

[25] Watson, Charles M., and Watson, James R.: Autotransfusion: Review of American Literature with Report of Two Additional Cases. Am. J. Surg., **33**, 232, 1936.

LIVER NECROSIS IN BURNS

F. W. Hartman, M.D., and H. L. Romence, M.D.

Detroit, Mich.

From the Departments of Pathology and Surgery, Henry Ford Hospital, Detroit, Mich.

Bardeen (1898) described "focal degeneration in the lymphatic tissues, liver and advanced parenchymatous degeneration of the kidneys" in autopsies upon five children with extensive burns. Weiskotten (1919) found focal necrosis of the liver in two of ten burn autopsies. Pack (1926), after a comprehensive review of the subject, stated that "there are no internal or visceral lesions pathognomonic of burns and scalds." Wilson (1935) attributed severe necrotic or fatty degeneration of the cells at the center of the liver lobule to the acute toxemia following severe burns. A further study of 33 cases, by Wilson, MacGregor and Stewart (1938), compared the liver lesion in burns to acute yellow atrophy.

McClure (1939), and McClure and Lam (1940) reported marked jaundice in clinical cases, with marked central necrosis of the liver in a case which failed to survive. Belt (1939) compared the midzonal necrosis of the liver found in four fatal burn cases to the liver lesions of yellow fever because of the demonstrated Councilman bodies and intranuclear inclusions. Wells (1940) was probably the first to offer objective data, suggesting that the tannic acid treatment might be the cause of liver necrosis, when he reproduced the lesion in rabbits by intraperitoneal and subcutaneous injections of tannic acid.

As a part of a study on burns projected by the National Research Council,* and carried out at the Henry Ford Hospital, further experimental study of liver damage was undertaken in an effort to determine:

1. The effect of the burn alone on the liver.

2. The effect of various types of protein coagulating chemicals, including tannic acid, on the liver.

3. The effect of burns treated with protein coagulating chemicals on the liver.

4. The effect of tannates on the liver and the significance of their identification in the urine of tannic acid treated and injected animals.

EXPERIMENTAL STUDIES

The experiments were all performed upon dogs under morphine and ether, or morphine and chloroform anesthesia. Morphine was continued for 24 to 48 hours after the procedures routinely, and longer if needed for the

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Henry Ford Hospital.

Permission to publish this paper has been granted by the Committee of Medical Research of the Office of Scientific Research and Development.

FIG. 1.

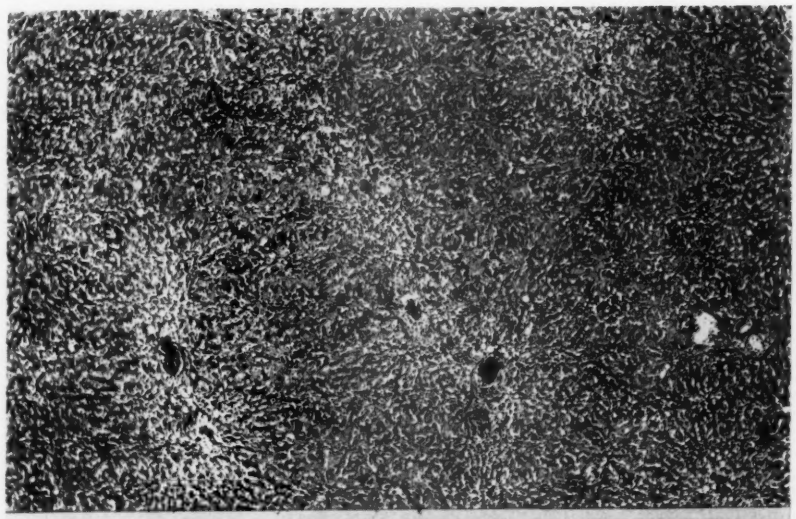


FIG. 2.

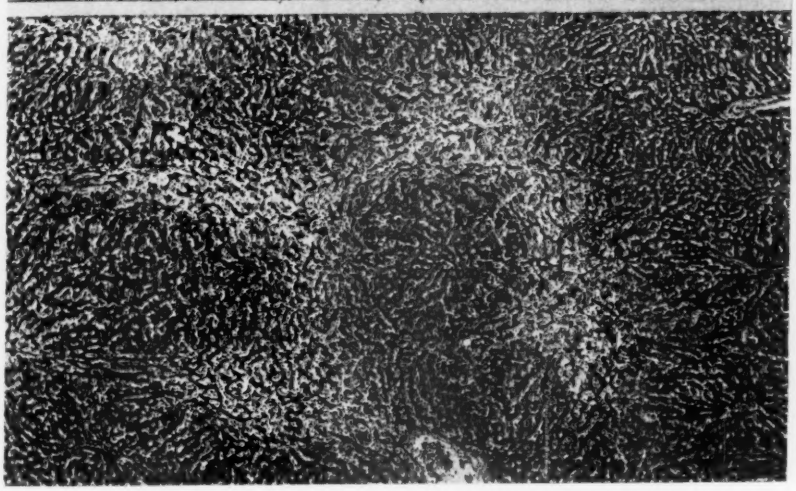


FIG. 1.—Dog. No. 3118: Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with sterile vaseline. Survival—10 days. Shows marked congestion, myelinization and necrosis at the center of the liver lobules. (Low power.)

FIG. 2.—Dog No. 3121: Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with vaseline scarlet R. Survival—9 days. Shows spotty necrosis about the center of the lobules with intense engorgement. (Low power.)

comfort of the animals. In case chloroform was used care was taken not to prolong the administration more than 15 to 20 minutes. The burns were produced with both dry heat and moist heat over 60 to 65 per cent of the body surface and were uniformly of third-degree severity.

GROUP 1.—To determine the effect of burns alone on the liver, the lesion was immediately dressed with neutral substances, sterile vaselined gauze

in 12 instances, lanolin in two instances, and normal salt solution in two instances.

In this group, 16 animals with large skin burns were used. The duration of life following the burn ranged from 4 to 20 days. The dressings, following the Koch method, were changed infrequently, if at all. The injured skin underwent maceration in 4 to 5 days and usually was the site of infection and suppuration. At autopsy, emaciation and anemia along with local and general infection were the usual findings. Grossly, the liver was enlarged, and in those living shorter periods, congested. The spleen was usually enlarged to 2 to 4 times the normal. Metastatic abscesses, with or without hemorrhages, were frequently seen. Curling's ulcers of the duodenum were produced in 5, or 33 per cent, of this group, and will be discussed in a later communication. Microscopically, the liver lesions ranged from marked suggestion of the sinusoids, with compression of the liver cords, to varying amounts of granular, vacuolar and fatty degeneration in experiments running 4 to 10 days, while myelinization and central necrosis was seen in those surviving 8 to 10 days (Figs. 1 and 2). The central necrosis in this series is a late development and associated with intense infiltration of the affected area. Although such lesions were accompanied by depression of liver function and icterus indices up to 20, the picture was not that of acute liver insufficiency.

GROUP 2.—To determine the effect of protein coagulating chemicals on the liver these substances were injected intraperitoneally and subcutaneously, and applied as a dressing to large surfaces from which the skin had been excised in 112 animals.

A. Silver Nitrate.—In this group, 15 animals were used, and all were injected subcutaneously with 2 per cent solution while the animals were under morphine and ether anesthesia. After injection morphine sulphate was given as indicated.

These animals survived the injection from 1 to 23 days. One animal died from distemper. Four animals lived only one day, but in all these marked, acute congestion of the liver, especially about the center of the lobule, was noted. Granular degeneration and early necrosis was seen in three. Two showed central necrosis of the liver of marked degree and extensive myelinization. Thus, 5, or 33.3 per cent, showed necrosis in varying degree but only 2, or 13.3 per cent, had extensive necrosis and myelinization, and these died on the eighth and eighteenth day, respectively. Eleven of the 15 died from the effects of the injection, and 4 were sacrificed because of ulceration (Figs. 3 and 4).

B. Alum.—Nine animals were used for the subcutaneous injection of aluminum and potassium sulphate. The 10 per cent solution was sterile and used in amounts ranging from 60 to 180 cc. The injections were all done under morphine and ether anesthesia. The length of life after injection ranged from 3 to 10 days, but five animals were sacrificed because of

ulceration and infection. Microscopically, the livers showed marked congestion and engorgement, with granular, and especially vacuolar degeneration. These degenerative changes obscure the cells near the center of the lobule but do not represent necrosis of cells such as seen in other groups.

C. Sulphosalicylic Acid.—Only six animals were used in this group, partly

FIG. 3.

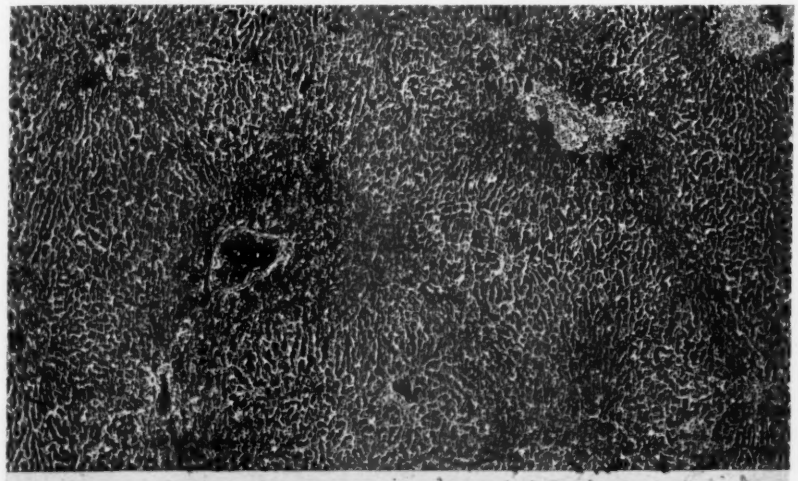


FIG. 4.

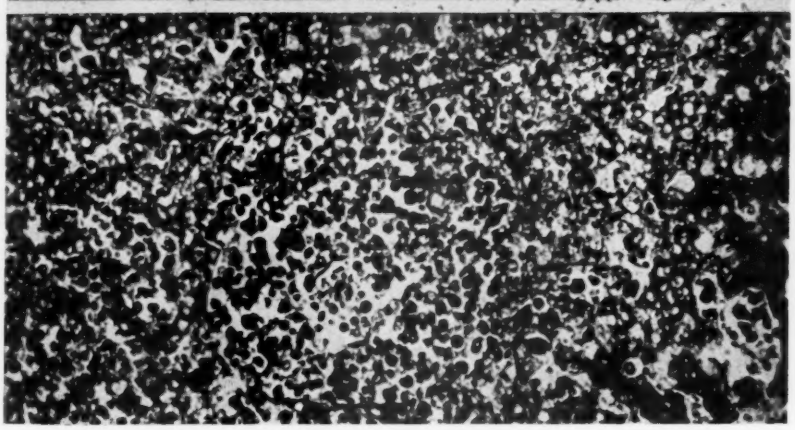


FIG. 3.—Dog No. 3126: Photomicrograph of liver from animal receiving 120 cc. silver nitrate 2% subcutaneously. Survival—5 days. Shows marked congestion, hemorrhage, and beginning necrosis at the center of the liver lobules. (Low power.)

FIG. 4.—Dog No. 3041: Photomicrograph of liver from animal receiving 100 cc. 2% silver nitrate subcutaneously. Survival—18 days. Shows central necrosis of liver lobule with intense myelinization. (Medium power.)

because the pathologic changes in the liver and other organs were minimal and partly because the sites of injection opened spontaneously and drained. Even the animals receiving from 120 to 140 cc. of 3 per cent solution, and surviving 7 to 10 days, showed congestion with early necrosis in two, and myelinization in one animal.

D. Zinc Peroxide.—In this group only five animals have been used to date. All were given subcutaneously suspensions of sterile ZnO_2 in sterile water; in the first instance 200 cc. of 7 per cent, and the other four 110 cc. of 22 per cent. These animals survived from 6 to 15 days. Three showed clinical jaundice with icterus indices from 15 to 35. Two showed central necrosis, while all showed congestion coupled with granular and vacuolar degeneration. The jaundice seen in this group is out of proportion to the necrosis seen in the liver but corresponds with the rapid weight loss and short duration of life.

E. Ferric Chloride.—Ferric chloride is one of the chemicals used as a tanning agent in the treatment of burns, hence it was included in this study both for subcutaneous injection and as a dressing for burned areas.

Thirteen animals were used for subcutaneous injection, 11 receiving from 100 to 175 cc. of a sterile 5 per cent solution, and two receiving 110 and 120 cc., respectively, of a sterile 10 per cent solution. Ten of the 13 died in from 1 to 5 days, and three were sacrificed after becoming moribund in 2 to 5 days. At autopsy, there was extensive greyish-yellow coagulation necrosis at the site of injection and extending around either side to the abdomen, associated with marked edema and blood extravasation. The hemorrhagic tendency was also seen at times in the pericardium and intestines. The liver was usually enlarged, mottled and dark red in color. Microscopic sections showed marked acute congestion with hemorrhage in seven animals and central necrosis in five, or in 38 per cent. This incidence of necrosis is somewhat higher than with tannic acid but the extent of the necrotic areas tends to be less. Hemorrhage, with and without necrosis, is more striking with ferric chloride than with tannic acid (Fig. 5).

F. Gallic Acid.—It has been suggested, from time to time, that gallic acid is toxic for the animal organism, at least that it is more toxic than tannic acid. This has been given as a reason for insistence on using only freshly prepared tannic acid solutions in the treatment of burns. Gallic acid, as a sterile 7.5 per cent solution, has been used five times for subcutaneous injection in amounts ranging from 110 to 150 cc. Microscopically, the livers of these animals showed principally acute congestion, hemorrhage and compression of the liver cells.

G. Quebracho Tannin.—Only four animals were used in this series because of the scarcity of material. The material used was the crude tannin* made up in a solution roughly comparable to the 7.5 per cent tannic acid, as far as the tannin content is concerned. This solution was injected subcutaneously in amounts ranging from 90 to 150 cc. The animals survived for periods ranging from 8 to 18 days. Clinical jaundice occurred once and, microscopically, central necrosis of the liver was found in two animals. Although this group is small it suggests that crude quebracho tannin has the same, or greater, possibilities for tannate absorption as tannic acid.

* Furnished by Parke, Davis & Co.

FIG. 5.

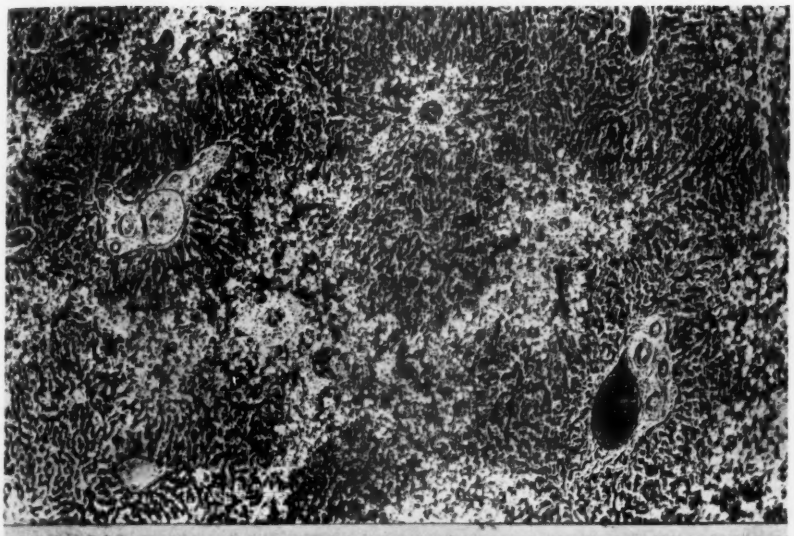


FIG. 6.

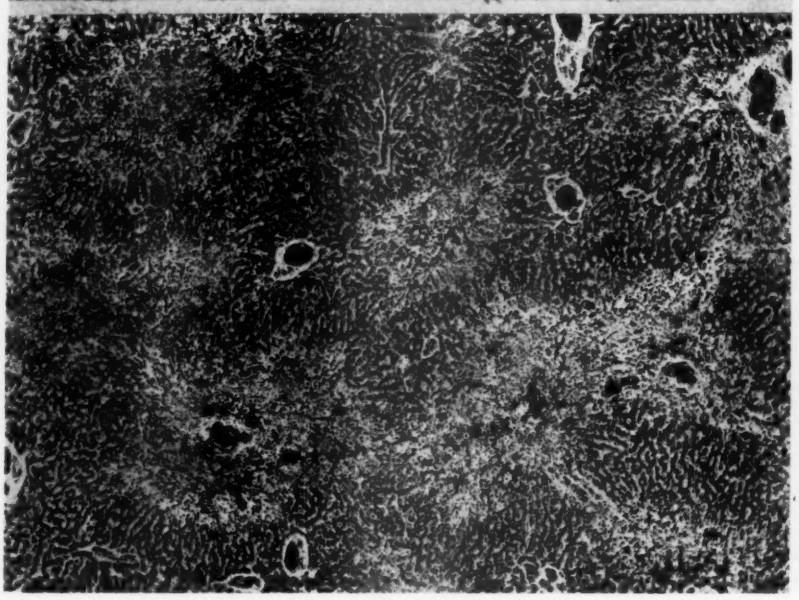


FIG. 5.—Dog No. 3160: Photomicrograph of liver from animal receiving 120 cc. of 10% ferric chloride subcutaneously. Survival—3 days. Shows extensive necrosis, fatty infiltration, and hemorrhage involving approximately one-third of the liver tissue. (Low power.)

FIG. 6.—Dog No. 3124: Photomicrograph of liver from animal receiving 150 cc. of 7.5% tannic acid subcutaneously. Survival—3 days. Shows very extensive central necrosis of liver lobules with hemorrhage. (Low power.)

H. Tannic Acid (used as intraperitoneal and subcutaneous injection).—In this group there are 41 experiments, each including the injection of sterile 7.5 per cent tannic acid solution. Six intraperitoneal and 33 subcutaneous injections were done. The intraperitoneal route was abandoned because of

the violent peritonitis produced and the short duration of life; however, central necrosis of the liver was seen twice, or in 33.3 per cent. With subcutaneous injections the dose ranged from 60 to 200 cc., depending upon the size of the animal. These injections were all done while the animals were under ether anesthesia, and were made at several points. The length of life after injection ranged from 2 to 16 days.

Autopsy showed extensive coagulation necrosis at the sites of injection and extending down the sides around the abdomen, especially with the larger doses. In five instances, 7.5 per cent tannic acid neutralized to p_H 7.4 with sodium bicarbonate was used subcutaneously, and the resulting coagulation and edema was comparable to that from the usual tannic acid at p_H 3.5.

None of the animals living less than two days showed necrosis of the liver, but marked acute congestion at the center of the lobule associated with granular and vacuolar degeneration predominated. In the 25 animals living 2 to 16 days, central necrosis of the liver was seen six times, or in 25 per cent, and extensive fatty degeneration twice, or in 8 per cent (Figs. 6, 7 and 8).

I. Tannic Acid Jelly (as dressing for areas from which skin was excised).—A group of three animals from which skin areas 20 x 20 x 16 inches were excised, had the denuded area dressed with sterile 7.5 per cent tannic acid jelly. These animals lived from 10–16 days. At autopsy, infection and suppuration was present in the wounds. Microscopically, the livers showed congestion, fatty degeneration and myelinization, but no central necrosis.

Analysis of the lesions obtained by the injection of these seven different chemical coagulating agents shows that the three most commonly used in the treatment of burns are the same ones responsible for the liver damage, namely, silver nitrate, ferric chloride and tannic acid.

The liver damage associated with the injection of silver nitrate developed relatively late and was accompanied by intense myelinization. Clinical jaundice and liver insufficiency were not produced with silver nitrate.

The liver damage occurring after the injection of ferric chloride was acute and hemorrhagic. The incidence was 38 per cent as compared with 25 per cent for tannic acid in the dosage-range used. Clinical jaundice was seen only twice in this group.

Central necrosis of the liver occurred in 33.3 per cent of animals receiving intraperitoneal injections of tannic acid and 25 per cent of animals receiving subcutaneous injections. The necrosis of the liver was produced more promptly and was more extensive than with the other coagulating chemicals. Clinical jaundice was seen on the fourth day and was progressive unless measures to combat it were instituted. The jaundice was accompanied by refusal of food, loss of weight and strength, vomiting, bloody stools, and coma.

GROUP 3.—To determine the effect of burns dressed with protein coagu-

lating chemicals on the liver, these chemicals were applied as dry dressings and as wet dressings to large skin burns in 31 animals.

A. Experiments with Skin Burns Treated with Tannic Acid Prepara-

FIG. 7.

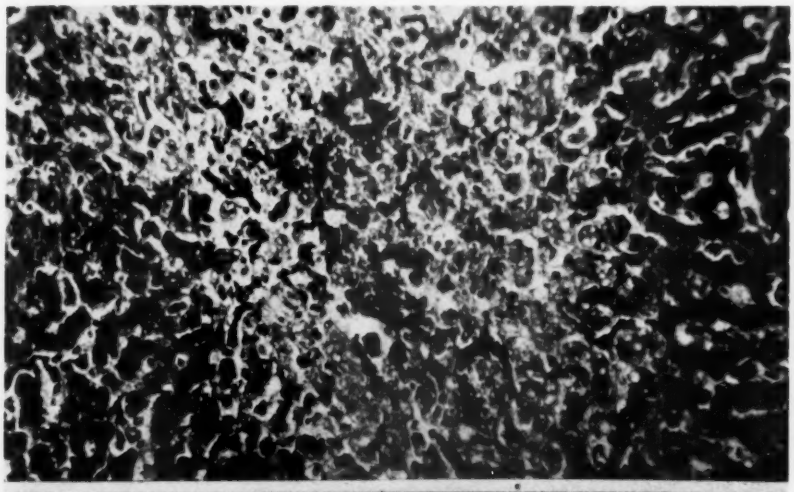


FIG. 8.

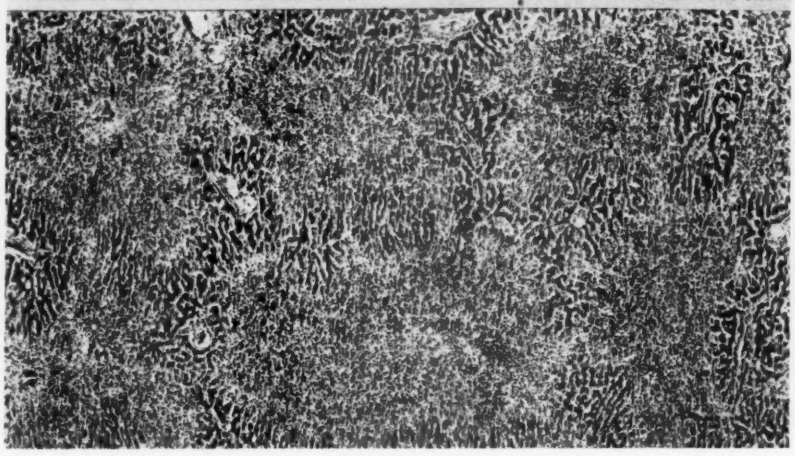


FIG. 7.—Dog No. 3124: Photomicrograph of liver from animal receiving 150 cc. of 7.5% tannic acid subcutaneously. Survival—3 days. The large lighter zone at the center shows complete lysis of liver cells with engorgement of the sinusoids and central vein. (Medium power.)

FIG. 8.—Dog No. 3161: Photomicrograph of liver from animal receiving 150 cc. of neutral tannic acid 7.5% subcutaneously. Survival—2 days. Central zone is necrotic, the liver cells being represented only by amorphous blue-staining material. The liver cells at the periphery also show degeneration so that they do not stain well. (Medium power.)

tions.—In the group of 24 animals, skin burns covering the entire back and sides were produced, ranging from 60 to 65 per cent of the body surface. In ten instances the burns were produced with a Bunsen burner and 14 times with a steam jet. The length of life was from 2 to 27 days. Clinical jaundice, with icterus indices ranging from 20 to 58, was seen in three animals,

or 12 per cent, and all these had a wet dressing with the tannic acid preparation. The urine from the animals with wet dressings was unusually dark in color and gave strongly positive tests for tannates.

Autopsy showed third-degree burns and good tanning in all, including those treated with neutral solution; but with the wet dressings the skin was macerated and usually suppurating. There was marked subcutaneous edema, especially over the abdomen, as in Dog No. 3170 (Fig. 9). Here it was noted that the edema fluid was blackened by the tannic acid, although the animal lived only 24 hours, suggesting that the tannate was absorbed especially when this plasma was reabsorbed. Metastatic abscesses of the kidneys were present in some cases. Central liver necrosis was present twice and central degeneration twice. In only one instance (Dog No. 3076) was necrosis associated with a dry dressing, and in this instance crude quebracho tannin was used as a spray (Fig. 10).

One animal, Dog No. 3142, with a fire burn, and a wet dressing of plain 7.5 per cent tannic acid jelly, passed blood from the intestinal tract for 24 hours preceding death, and was found to have a large Curling's ulcer, with blood clot attached, in the first portion of the duodenum.

FIG. 9.—Dog No. 3170: Had burn produced with steam jet covering 60% of the body surface, to which a wet dressing of 7.5% tannic acid jelly was applied. Survival—1 day. Shows penetration of the tannic acid dressing 1 cm. into the edematous subcutaneous tissue beneath the burn.

B. Experiments with Skin Burns Treated with 5 per cent Ferric Chloride. In this group 5 per cent sterile ferric chloride solution was used to dress and tan large burned areas of about 60 per cent of the body surface. Two burns so treated were produced with the Bunsen burner and three with the steam jet. This solution produced a good tanning in both types of burns after four to six applications over a 12- to 24-hour period—fully equal to that produced by tannic acid. Three animals had dry dressings and lived from 7 to 16 days before being sacrificed while still in good condition. Two in which wet dressings were applied died after 8 and 11 days, respectively. These two were the only ones in this series showing significant lesions in the liver, Dog No. 3141 showing extensive central necrosis with hemorrhage, and Dog No. 3145 showing marked fatty infiltration and congestion (Fig. 11).

In this group large skin burns were actually treated with tannic acid and ferric chloride preparations. Here, conditions similar to those present in the handling of clinical burns were reproduced. Clinical jaundice with icterus

FIG. 10.

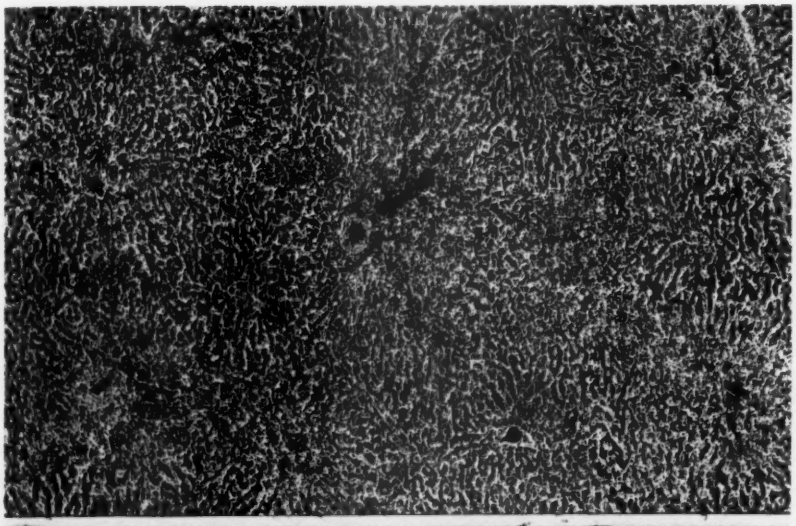


FIG. 11.

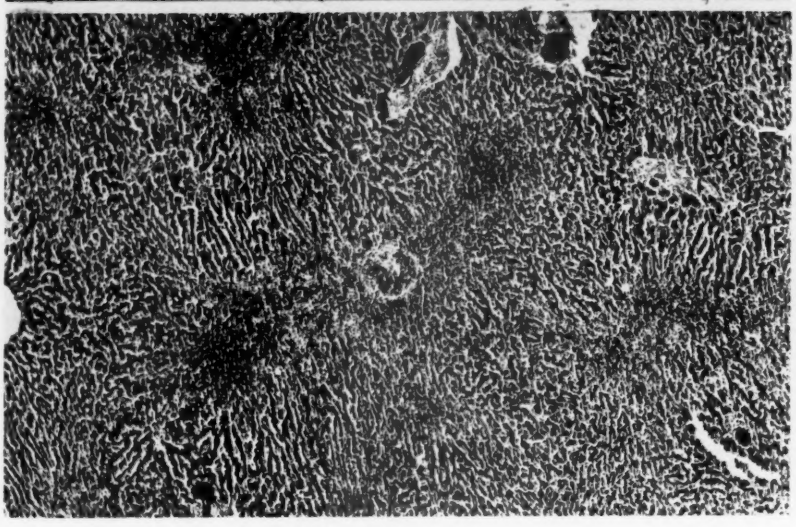


FIG. 10.—Dog No. 3176: Photomicrograph of liver from animal in which a burn was produced with steam jet covering 60% of the body surface, to which a wet dressing of 7.5% tannic acid in cetyl alcohol base was applied. Survival—11 days. Shows marked congestion and hemorrhage with central necrosis. (Low power.)

FIG. 11.—Dog No. 3141: Photomicrograph of liver from animal in which approximately 60% burn was produced with steam jet and dressed with 5% ferric chloride jelly. Kept wet with pliofilm covering. Survival—8 days. Shows marked engorgement of blood vessels with necrosis and hemorrhage at the center of the lobule involving approximately 40% of the liver tissue. (Low power.)

indices ranging from 20 to 58 was seen in three animals, or 12 per cent, all of which had wet dressings rather than the usual drytanned eschar. Central necrosis and degeneration was found in four, or 16 per cent. Only one of these had a dry dressing, and that consisted of crude quebracho tannin applied as a spray.

On the basis of these findings, wet dressings and baths of tannic acid will give us the highest incidence of liver necrosis and should be avoided, as pointed out by Davidson in his original contributions.

GROUP 4.—To determine the effect of tannates on the liver, blood plasma was precipitated with tannic acid, twice washed, and injected subcutaneously. Alkaline sodium tannate solution p_H 9 was injected intravenously. Tannates and gallates excreted in the urine were identified.

It had been assumed that tannic acid with a p_H of 3 combined with proteins formed an insoluble compound which would be inert in the body. However, such compounds were prepared using blood plasma as the source of protein and the twice washed precipitate was injected subcutaneously in 100 to 120 cc. amounts of the 50 per cent suspension. Two of the four animals injected showed early central necrosis of the liver, suggesting at least that the material was absorbed and was toxic for the liver (Fig. 12). Following this experiment it was observed that tannic acid was absorbed into the edematous subcutaneous tissues beneath the burned tanned skin for a distance of 1.5 cm., as evidenced by the brownish-black discoloration. Then the dark brownish urine excreted by both the animals injected subcutaneously with tannic acid preparations and those burned and dressed with the same preparations, were shown to contain tannates, as identified by Dr. V. Schelling. Neutralized tannic acid and quebracho tannin used for subcutaneous injection and dressings excreted relatively large amounts of tannates and gallates.

Detection of Tannates in Urine. —Tannates excreted in urine are demonstrated by the bluish-black color with ferric chloride. Since, however, gallic acid, a hydrolysis product of tannic acid, gives the same color, a more specific reagent is required. Sanin's reagent (Merck's Index, 5th edition, p. 808) fulfills this requirement. It gives a white precipitate with tannic acid but no precipitate with gallic acid.

Some urines which gave a positive ferric chloride reaction did not precipitate with Sanin's reagent, indicating that gallates were present in these urines. The kidney, according to Sieburg and Mordhorst, does not possess an enzyme system that is capable of splitting tannins. However, the liver, according to these authors, might be the site where splitting of tannins occurs.

Attempts were made to use Folin and Denis phenol reagent for a more quantitative evaluation of tannates in urine. All urines which gave a positive ferric chloride reaction developed a blue color with this reagent after treatment with silver-lactate-NaCl-HCl. However, the color developed was different for each urine and could not be matched adequately with the color of the standard prepared from tannic acid.

Although neutralized tannic acid proved quite effective in the coagulation of proteins, both *in vitro* and *in vivo*, alkaline sodium tannates with p_H 9 failed to coagulate proteins so that it became possible to inject such solutions directly into the blood stream of both rabbits and dogs without immediate

or delayed reaction. Two dogs of 7 and 8 kilos were given 15 cc. of 7 per cent sodium tannate solution intravenously. These animals excreted brownish urine containing tannates, and showed a rapidly deepening jaundice at the end of 48 hours. One animal died in 48 hours in deep coma, with

FIG. 12.

FIG. 13.

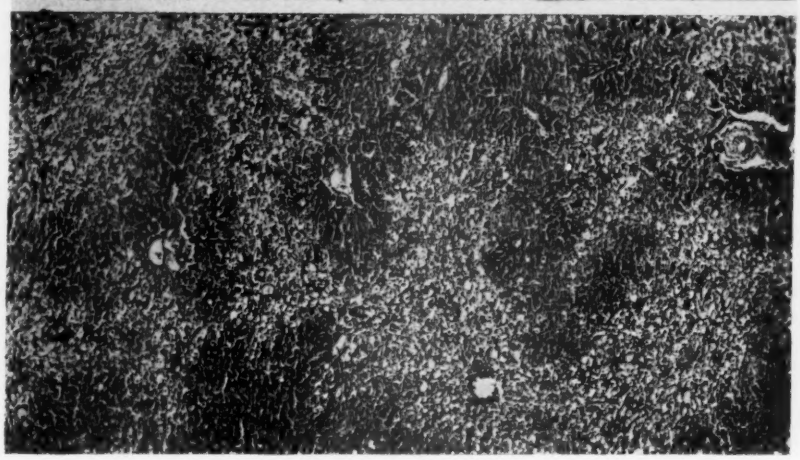


FIG. 12.—Dog No. 3137: Photomicrograph of liver from animal receiving 100 cc. of twice washed protein tannate subcutaneously. Survival—3 days. Shows extensive central necrosis of liver lobule. (Low power.)

FIG. 13.—Dog No. 3193: Photomicrograph of liver from animal receiving 15 cc. of 7% sodium tannate solution intravenously. Survival—3 days. Clinical jaundice marked. Icterus index 140. Shows vacuolar degeneration and necrosis of liver cells about the centers of lobules. (Low power.)

an icterus index of 140 (Fig. 13). The second lived a week, with increasing jaundice, marked listlessness, and refusal of food. Autopsy of these animals showed a small, brownish-green liver that was flabby and soft and friable

on section. The usual lobulation could not be made out. Microscopically, there was acute central necrosis of 50 per cent of the liver tissue.

Rabbits of 3 and 4 kilos were given 8 cc. of the 7 per cent sodium tannate solution into the marginal ear vein. No jaundice was detected either clinically or at autopsy, but all succumbed in two to six days. Microscopically, the livers showed more marked central necrosis than those of the dogs receiving this solution. Only a fringe of liver cells remained at the periphery of the lobule while the centers were necrotic and hemorrhagic (Fig. 14).

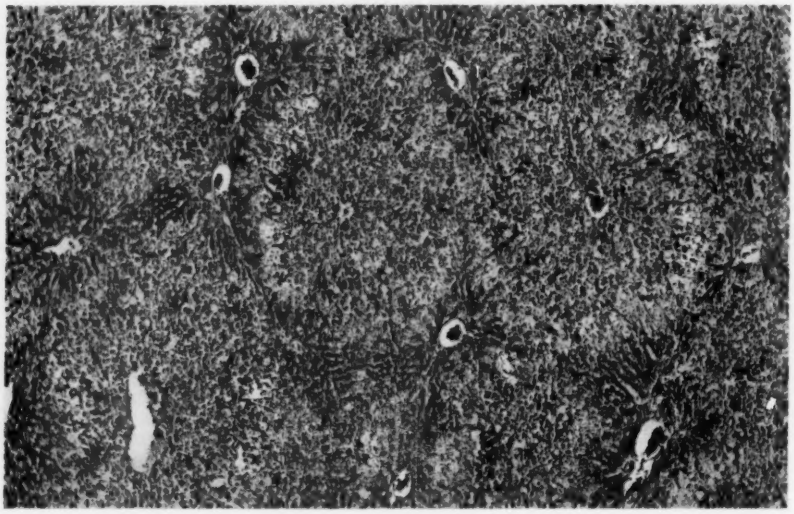


FIG. 14.—Rabbit No. 3195: Photomicrograph of liver from animal receiving 7 cc. of a 7% sodium tannate solution intravenously. Survival—24 hours. Shows complete lysis of the cells of the liver lobule with the exception of a fringe about the periphery. (Low power.)

The production of liver necrosis by the subcutaneous injection of washed tannates and the intravenous injection of alkaline sodium tannate solutions demonstrates the etiologic importance of tannates in the pathogenesis of this lesion. Further the identification of relatively large amounts of tannates and gallates in the urine excreted by animals burned and treated with tannic acid preparations, as well as in the urine of those injected with tannic acid subcutaneously, shows that these tannates are absorbed from the site of treatment or injection into the blood stream. This fact being established, it is clear that the liver cells may be destroyed just as they are when tannates are injected intravenously.

SUMMARY AND CONCLUSIONS

1. Large experimental burns result in marked engorgement of the sinusoids of the liver, especially about the central veins, and compression of the liver cells in this area.

2. Acute compression of the liver cords is followed even in the groups treated with sterile vaseline and sterile salt solution by granular, vacuolar

and fatty degeneration. With longer survival, especially if infection either in the form of pneumonia or suppuration of the burned area occurs, actual necrosis of liver cells at the center of the lobule, with myelinization, may be seen.

3. Introduction of any of the coagulating agents mentioned, either as a dressing for a burned or denuded area, or as a subcutaneous injection, increased the incidence of degeneration and necrosis of liver cells, with or without hemorrhage.

4. Oddly enough, the three coagulating agents that have been used in the treatment of burns are the only ones that have, in this work, increased the danger of clinical jaundice and liver insufficiency. These chemical agents are in order of importance: Tannic acid; ferric chloride; and silver nitrate.

5. Tannic acid used as a wet dressing for burns has produced clinical jaundice in the dog in 12 per cent and central necrosis of the liver in 16.5 per cent. In only one instance was liver necrosis seen associated with the dry tanning of a burn, and in this crude quebracho tannin was used.

6. Tannic acid used as a subcutaneous injection in a series of 25 animals has produced liver necrosis in 25 per cent. With intraperitoneal injection, in a series of six, liver necrosis was produced in two, or 33.3 per cent.

7. Quebracho tannin and tannic acid neutralized with sodium bicarbonate in a small series were more potent than tannic acid in the production of liver damage.

8. Animals having burns treated with wet dressings of tannic acid or tanning preparations and those receiving subcutaneous injections of these preparations, excrete relatively large amounts of tannates and gallates in the urine. These groups have the highest incidence of liver necrosis.

9. Sodium tannate of p_H 9 does not coagulate protein readily and may be given in amounts of 10 to 20 cc. of the 7 per cent solution daily without reaction. Such injections in four rabbits and five dogs have resulted in the consistent production of liver necrosis in both groups with clinical jaundice and death in the dogs.

10. The excretion of tannates in the urine of animals receiving wet dressings or injections of tannic acid, coupled with the fact that these animals along with those receiving tannates intravenously have a high incidence of jaundice and liver necrosis, shows the etiologic relation of these tannates to the liver lesions.

11. Silver nitrate used in 2 to 10 per cent sterile aqueous solution subcutaneously, produces extensive necrosis and edema at the site of injection, with some degeneration, hemorrhage, and necrosis of the liver. However, clinical jaundice has not occurred, and death could not be charged to the grades of liver damage seen.

12. Ferric chloride used in 5 to 10 per cent sterile aqueous solution subcutaneously, produces marked necrosis, edema, and hemorrhage at the site of inoculation. Clinical jaundice does occur, and the extensive central

necrosis and hemorrhage in the liver must be listed as one of the causes of death. A single animal with a wet dressing of ferric chloride on its 60 per cent burn died on the eighth day and showed liver necrosis, with hemorrhage.

REFERENCES

1 Bardeen, C. R.: A Review of Pathology of Superficial Burns with a Contribution to our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns. Johns Hopkins Hospital Rep., **7**, 137–179, 1898.

2 Weiskotten, H. G.: Histopathology of Superficial Burns. J. A. M. A., **72**, 259–261, January 25, 1919.

3 Pack, C. T.: The Pathology of Burns. Arch. Path., **1**, 767, 1926.

4 Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds under Modern Treatment. Brit. Jour. Surg., **25**, 826, 1938.

5 McClure, R. D.: The Treatment of the Patient with Severe Burns. J. A. M. A., **113**, 1808–1812, November 11, 1939.

6 McClure, R. D., and Lam, C.: Problems in the Treatment of Burns. Southern Surg., **9**, 223–234, April, 1940.

7 Belt, Thomas H.: Liver Necrosis Following Burns; Simulating the Lesions of Yellow Fever. Jour. Path. & Bact., **48**, 493–498, May, 1939.

8 Wells, D. B.: Panel Discussion on Burns. American College of Surgeons Meeting, Chicago, October 24, 1940.

9 Davidson, Edward C.: Tannic Acid in the Treatment of Burns. Surg., Gynec. & Obst., **41**, 202–221, 1925.

10 Sieburg, E., and Mordhorst, G.: Distribution of Enzymes in the Animal Organism which Decompose Tannin and Related Compounds. Biochem. Ztschr., **100**, 204, 1919.

ANIMAL EXPERIMENTS WITH TANNIC ACID

Suggested By the Tannic Acid Treatment of Burns

Roger Denio Baker, M.D., and Philip Handler, Ph.D.

Durham, N. C.

From the Departments of Pathology, Physiology and Pharmacology, Duke University School of Medicine, Durham, N. C.

Since about 1925,[1] tannic acid has been widely used in this country and abroad[2] in the treatment of cutaneous burns, by spraying on aqueous solutions, by bathing the patient in aqueous solutions, or by applying an ointment to the burned area. The concentrations of tannic acid in the preparations which have been employed have ranged from less than 5 to 20 per cent. The U. S. P. tannic acid ointment has been made up with 20 per cent tannic acid, but in a tubed preparation recently acquired the tannic acid content is five per cent.

The local effects of the tannic acid have been advantageous in several respects. Pain has been relieved, a firm, dry coating or eschar has formed, and the nursing problem has thereby been rendered simpler. The dryness of the eschar, and probably some of the properties of the tannic acid, have inhibited bacterial growth. The disadvantages of tannic acid in the area of application have been pointed out.[3] These include: (1) Cracking of the stiff eschar, and curling of the edges; (2) too great stiffness of the eschar if the substance is applied to the face or perineum; and (3) masking by the eschar of underlying infection. In addition, tannic acid may destroy remnants of epidermis and hair follicles from which skin might regenerate in the stage of healing.[4] The eschar may be difficult to remove.

The most serious drawback to the use of tannic acid to date is the suggestion that it is absorbed from the region of application and causes damage to the liver.[5, 6] Since 1938, at least four communications[2, 5, 7, 8] have appeared describing impressive central necrosis of the liver in patients who have been burned and have had some form of tannic acid therapy, whereas papers on fatal burns which appeared before the use of tannic acid do not emphasize hepatic necrosis as characteristic of burns.[9, 10]

Evidence has begun to accumulate that tannic acid damages the livers of animals when it is absorbed from a burned area or from the subcutaneous tissues. Dogs burned experimentally and then treated with tannic acid ointment showed hepatic necrosis,[8] but, since no control experiments were performed in which tannic acid was applied in the absence of the burn, the comparative rôle of burn and tannic acid in the production of hepatic necrosis is difficult to evaluate. Following subcutaneous injections of tannic acid (U. S. P.) into white rats severe hepatic damage has been observed.[5]

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University. Aided by the Duke University Research Fund.

† One of us (P. H.) is indebted to the John and Mary Markle Foundation for its support.

These lesions consisted of central necrosis comparable to that noted in autopsies of burned patients who had been treated with tannic acid; and the degree of liver damage in the rats was in direct proportion to the amount of tannic acid injected subcutaneously. Some of the rats (70–90 Gm.) which received a total dosage of from 0.15 to 0.4 Gm. of tannic acid during a day or two, died within this period, while others were sacrificed on the third or fourth day, and usually showed hepatic necrosis. It was also stated that similar results were obtained after the injection of rabbits and guinea-pigs with tannic acid.

EXPERIMENTAL STUDIES

In the experiments to be reported it was desired to amplify those made on rats already mentioned,[5] and to determine the importance of the various factors involved, in order to judge the applicability of tannic acid to the treatment of human burns, insofar as the experimental results might aid in the settling of this problem.

The following four series of experiments were undertaken, and will be considered subsequently under each heading:

(I) Experiments to verify the observation[5] that subcutaneous injections of tannic acid produce hepatic necrosis.

(II) Experiments to determine whether tannic acid is absorbed when applied to a body surface denuded of skin.

(III) Experiments to determine whether tannic acid or some derivative thereof, can be excreted in the urine, after the subcutaneous injection of tannic acid.

(IV) Experiments to determine whether tannic acid (U. S. P.) can be purified further, so as to avoid hepatic damage.

I—HEPATIC NECROSIS FROM SUBCUTANEOUS INJECTIONS OF TANNIC ACID

In rats, subcutaneous injections of solutions of tannic acid (U. S. P.—Merck) produced hepatic necrosis, thus corroborating the experimental results in rats obtained by Wells, Humphrey, and Coll,[5] previously mentioned. For example, in a test with 11 rats (34–58 Gm. each) tannic acid injected in divided doses subcutaneously, the total amount varying from 50 to 150 mg., caused the death of four rats in 1 to 3 days. In those rats which survived and were sacrificed, microscopic study of the organs showed central necrosis of the liver; while microscopic study of the organs of five control rats injected subcutaneously with distilled water showed no necrosis of the liver. In addition, it was found that there was much necrosis at the point of injection of the tannic acid, and much inflammatory reaction, while no necrosis and minimal inflammation occurred at the point of injection of distilled water in the controls. (In no experiments were the solutions sterilized)

Exactly the same type of experiments were carried out in 115 white mice (Table I), with the same results. It is seen that as little as 0.5 cc. of

0.5% aqueous solution (2.5 mg. of tannic acid) produced hepatic necrosis and necrosis at the point of injection. The use of this concentration, similar to the use of greater strengths, resulted in the death of many mice. Of 30 control mice which received distilled water, only one showed any hepatic necrosis and none died. It seemed fair to conclude, therefore, that subcutaneous injections of tannic acid were often lethal for mice, and that hepatic damage was frequently produced. None of the other organs examined (heart, lungs, spleen, kidney) showed lesions.

TABLE I

EFFECT OF SUBCUTANEOUS INJECTIONS (0.5 CC. PER INJECTION) OF TANNIC ACID (U.S.P.) ON WHITE MICE (12-30GM.)

No. of Mice	Tannic Acid	No. of Injections	No. Died	Killed after	Total Dose	Local Necrosis	Lesion Inflammation	Liver Necrosis	Lesion Fatty Change
5	10%	1 or 2	4	2 days	50-100 mg.	++++	+	++	0
8	5%	1 or 2	5	2 days	25-50 mg.	+++	+	+	0
18	2.5%	1 or 2	11	2 days	12.5-25 mg.	++	++	++	±
19	1%	1 or 2	9	2 days	5-10 mg.	++	++	++	±
20	0.5%	1 or 2	10	2 days	2.5-5 mg.	++	++	++	±
15	0.25-0.5%	4	0	4 days	6 mg.	±	+++	0	+
				CONTROL MICE RECEIVING DISTILLED WATER					
17		1 or 2	2	2		±	±	0	±
1		2	0	2		+	+	+	+
12		4	0	4		0	0	0	+

In Table I it is to be noted that the sublethal dosage was in the neighborhood of 0.5 cc. of a 0.25% tannic acid solution. This amount could be given repeatedly without causing death or hepatic change, visible microscopically. Of mice which survived after receiving larger doses and which were sacrificed after two days, the great majority showed central necrosis of the liver of varying degree (++ indicates that necrosis was complete from the central vein outward for one-third of the radial distance to the periphery of the lobule). In some mice, allowed to survive much longer (not shown on Table I), hepatic lesions were not found, and it was thought that lesions had probably been present during the first several days and had then repaired by regeneration. However, carefully controlled experiments to prove this point were not successfully concluded. From general knowledge concerning the regenerative power of the liver, it seems probable that this is true.

Acidity of Tannic Acid Not the Necrotizing Factor.—That the necrotizing effect of tannic acid at the area of application and in the liver was not due to the acidity of the drug, is shown by the results of injection of neutralized tannic acid as shown in Table III. Tannic acid (5%), brought to p_H 7.2, produced well-marked necrosis at the point of application and in the liver, nearly as marked as the original 5% tannic acid of p_H 3. In addition, hydrochloric acid was adjusted to p_H 3 with sodium hydroxide, and when injected had no necrotizing effect on the liver, and only slight effect locally at the site of injection.

II—ACTION OF TANNIC ACID APPLIED TO A BODY SURFACE DENUDED OF SKIN

Unsuccessful attempts were made to duplicate exactly in the rat the therapeutic use of the drug on human burns. Burns were made by various

methods (flame, soldering iron, scalding, *etc.*) but were unsatisfactory for experimental purposes for three reasons: (1) The burn frequently affected the viscera through the thin wall of the rat; (2) the exact size of the burn could not be standardized; and (3) when the burn was large enough for test purposes the rats sometimes died from the direct effect of the burn.

Because of these drawbacks, no study has been made of the absorption of tannic acid from a burn, but data have been secured concerning the absorption of tannic acid from body surfaces denuded of skin. Such data are important because the burn is excluded as a complicating factor. But the inference should be carefully avoided that absorption from a burned area would be the same as from these experimentally produced wounds. Burns often have a layer of necrotic tissue which might produce conditions far different with regard to the local and distant effects of tannic acid. Moreover, in certain burns the epidermis may not be destroyed, and there is evidence that the horny layer of epidermis may act protectively against tannic acid.[4]

If all of the skin of the thorax and abdomen were removed, in a zone encircling the trunk, the rats died of this procedure alone, too soon for any further experimentation. However, by denuding the skin of the ventral surface of the abdomen and thorax, over an area of about 8 x 10 cm. in large rats, the rats survived satisfactorily. Such an area, untreated, remained moist for a time, and was usually somewhat moist after two days, when the control rats were sacrificed. The denuded areas had usually contracted somewhat by this time.

The procedure consisted of anesthetizing the rat with ether, denuding the ventral skin, and suspending the rat in the solution to be tested (tannic acid solution, distilled water, *etc.*) for 15 minutes, while the animal was still under the influence of ether. The amount of skin removed was always less than one-third of the whole body surface, usually about one-fifth or one-quarter. The following day the denuded area was washed with the test solution, without anesthesia of the rat, and at the end of the second day the rat was sacrificed with illuminating gas. When ointment was employed, it was thoroughly applied to the denuded area of the anesthetized rat and again on the following day, without anesthesia of the rat.

In experiments not included in Table III, it was demonstrated that the shaved body surface or the severely scratched body surface did not permit the absorption of enough tannic acid to produce any hepatic necrosis. Also, it was shown that soaking the animal in tannic acid solution for 15 minutes produced no necrosis of the undamaged epidermis. This is probably due to the protective effect of the stratum corneum and the more superficial layers of the epidermis, as emphasized by Taylor[4] (who was able, however, to produce epidermal necrosis by repeated exposure to tannic acid over a period of several hours).

The experimental results following application to the denuded body

surfaces are shown in Table II. A few rats died apparently as the result of the treatment with the stronger aqueous solutions of tannic acid. (Two of the rats treated with 20% tannic acid, and the control rat treated with distilled water, were judged to have died because too much skin was removed).

TABLE II

EFFECT OF TANNIC ACID APPLIED TO RATS PARTIALLY DENUDED (LESS THAN ONE-THIRD OF BODY SURFACE) OF SKIN. RATS (136-398 GM.) SACRIFICED ONE TO FOUR DAYS AFTER FIRST APPLICATION

		Area			Local Lesion			Liver Lesion		
Treatment	No. of Rats	Denuded, at Autopsy	No. Died	Killed after	Necrosis	Inflammation	Bact. Growth	Necrosis	Fatty Change	Mitosis
20% solution	16	35 sq. cm.	5	1-4 days	++++	+	+	±	+	0
20% ointment	6	35 sq. cm.		2 days	++++	+	+	++	+	±
15% solution	3	46 sq. cm.	1	2 days	++++	+	±	+++	+	++
10% solution	3	54 sq. cm.		2 days	++	+	±	+	±	0
5% solution	3	54 sq. cm.		2 days	+	+	±	+	±	±
5% ointment	3	53 sq. cm.		2 days	+	+	0	±	+	+
5% solution and 10% $AgNO_3$	3	37 sq. cm.		2 days	++++	+	0	0	+	0
2.5% solution	3	51 sq. cm.		2 days	+	+	±	±	±	0
Distilled water	28	40 sq. cm.	1	2-4	±	+++	+++	0	+	0

Effect upon the Liver.—Hepatic necrosis was usually, but not invariably, produced whether the aqueous solution or the ointment was used. There were individual variations among the rats. For example, the necrosis was of a high degree in one of the rats treated with 15% aqueous solution, the central three-fourths of each lobule being destroyed, while in the other two rats, which received this solution, the necrosis extended out about one-quarter of the distance from the central vein to the periphery of the lobule. None of the controls treated with distilled water showed any hepatic necrosis. In general, the hepatic damage produced was less severe than from small subcutaneous injections, a result which is perhaps not surprising, since the subcutaneous material might be absorbed into the lymphatics and blood vessels, and this absorption might go on for some time.

No hepatic necrosis was noted in the three rats treated with 5% tannic acid and 10% $AgNO_3$, applied alternately over a period of 30 minutes, with omission of all treatment on the following day.

There was no correlation between fatty change and the concentration of tannic acid. Mitoses were noted more often in the hepatic cells of livers which had been severely injured. No lesions were noted by microscopic examination in other organs (kidney, spleen, lungs, heart) which were examined routinely.

In a separate test on four rats, it was found that the application of a strong (20%) solution of tannic acid to small areas (6 sq. cm.) denuded of skin was attended with no hepatic necrosis.

Effect of Tannic Acid at Site of Application.—Tannic acid often had a direct necrotizing action on living tissue when applied to a free subcutaneous or muscular surface. It was thought to coagulate the protein in the living cells at the site of application. A local effect of tannic acid on living cells has previously been claimed.[4]

Proof of the necrotizing action of tannic acid was obtained by comparing microscopic sections of the denuded abdominal wall of rats treated with tannic acid preparations with corresponding sections from rats treated with distilled water alone.

When distilled water alone was used there was, of course, some superficial necrosis of the denuded surface, due to the drying of the tissues, and other traumatizing factors and possibly early bacterial action. However, in the great majority of rats treated with distilled water the necrosis did not extend through the fibrous sheath overlying the abdominal muscles to involve the muscle fibers. In the rats treated with tannic acid preparations, necrosis of this underlying muscle was usually noted, and sometimes it was severe. The necrosis of muscle resulting from immersion of the rat in 20% tannic acid, for example, extended, on the average, one-fourth of the way through the abdominal muscle mass in the denuded area. Necrosis from weaker preparations, 2% and 5%, was at times no greater than that caused by distilled water, but in most cases was greater. In the three rats treated with 5% tannic acid and 10% silver nitrate, the local effect on the muscle was about the same as that from the 20% tannic acid preparations, but only three rats were treated with the combined drugs. Associated with the necrosis there was cellular inflammatory reaction and edema of the adjacent tissues. This was usually less prominent than in the rats subjected to distilled water. Bacterial growth was not demonstrated deep in the tissues in microscopic sections in any of the rats, but in the rats treated with distilled water bacterial growth on the surface was regularly far greater than in the rats treated with tannic acid preparations.

III—METABOLITES IN URINE

A material which gave the ferric chloride test for tannic acid and gallic acid was demonstrated in the urine of rats which had received tannic acid subcutaneously. The exact nature of the substance could not be demonstrated, but the substance was not in the urine of normal controls injected subcutaneously with distilled water.

Rost,[11] in 1897, concluded from studies on cats and rabbits that tannic acid administered intravenously or subcutaneously does not pass unchanged into the urine, but appears as gallic acid and, apparently, also in the form of other, as yet unknown, products of tannic acid.

Tannic acid solution (1 cc. of 5% solution) was injected with great care to prevent spilling, beneath the shaved skin of anesthetized (ether) rats. Urine was collected for 24 hours in a metabolism cage. As controls, distilled water was injected into anesthetized rats and the urine collected in the same fashion.

The urine from the rats which had received the tannic acid turned black or dark gray when ferric chloride (10%) was added, while the urine from the normal rats did not give this reaction. The possibility that a small quan-

tity of tannic acid had escaped from the injection site and had contaminated the collected urine was checked on by obtaining urine directly from the urinary bladder of one of the rats. The possibility that the material excreted was acetone bodies was excluded by means of a negative Rothera test for acetone; and the possibility that it was aceto-acetic acid was excluded by boiling the urine, thus destroying any aceto-acetic acid, and then obtaining the darkening of the urine on the addition of ferric chloride.

The darkening of the urine produced by ferric chloride in the rats injected with tannic acid matched the darkening produced in 0.1% aqueous solution of tannic acid, U. S. P., (or in 0.1% normal urine solution of tannic acid, U. S. P.). Attempts to show that the material in urine from the rats which had received tannic acid was tannic acid by the precipitation of egg albumen were unsuccessful. *In vitro* experiments with tannic acid in normal urine, however, indicated that the urine, apparently, would inhibit the precipitation of egg albumen by tannic acid. Attempts to identify the material by absorption spectra were also unsuccessful, as were several other tests for tannic acid.

TABLE III

THE EFFECT OF GALLIC ACID AND OF THE ACIDITY OF THE EXPERIMENTAL SOLUTIONS UPON WHITE RATS (SUBCUTANEOUS INJECTIONS, 1 CC. DAILY; TOTAL DOSE 100 MG. (ALL RATS SACRIFICED AFTER TWO DAYS)

No. of Rats	Local Lesion			Liver Lesion	
	Necrosis	Inflammation	Necrosis	Fatty Change	Mitosis
		5% gallic acid (p_H 3)			
6	++	++	0	0	±
		5% neutral gallic acid (p_H 7.2)			
6	+	++	0	±	0
		5% neutral tannic acid (p_H 7.2)			
6	+++	++	++	±	±
		HCl acid (p_H 3)			
3	+	++	0	±	0
		5% tannic acid (p_H 3)			
5	+++	+++	+++	±	++

Since gallic acid is a decomposition product of tannic acid, and since it has been stated to appear in the urine of cats and dogs given intravenous or subcutaneous tannin,[11] tests were made with this crystalline substance, to see how closely it resembled tannic acid in its effects on rats. Rats injected with gallic acid produced urine which gave an intense ferric chloride reaction.

However, evidence was obtained that gallic acid was not the portion of tannic acid responsible for hepatic necrosis (Table III), for when 5% gallic acid was injected subcutaneously (100 mg.) no hepatic necrosis was obtained.

In brief, it was demonstrated that the urine of rats which had received tannic acid subcutaneously blackened when ferric chloride was added. Thus, while the phenolic substance in these urines has not been positively identified, there is presumptive evidence for the circulation of tannic acid or its derivatives in these rats. In any analysis of the mechanism of the production of hepatic necrosis this factor must be considered. Moreover, the necrotizing effect of tannic acid on the liver was probably not due to the gallic acid component of tannic acid.

IV—ATTEMPTS TO PURIFY TANNIC ACID

It was desired to determine whether or not the effects of tannic acid (U. S. P.) on rats and mice were due to the tannic acid itself or to extraneous substances present in this material. Accordingly, several attempts to obtain crystalline tannic acid were made in the following manner: To 25 cc. of two-thirds saturated tannic acid were added 15 volumes of saturated sodium chloride solution. The tannic acid was kept in a bath maintained, in consecutive experiments, at −10°, 0°, 10°, 25°, 37° C. The sodium chloride was added drop-wise over the course of eight hours in all but two instances. The experiments at 0° and 25° C. were continued for 24 hours. The sample of tannic acid which precipitated in each trial was used again in the next trial. In no case was a crystalline product obtained, although the samples were contaminated with considerable quantities of sodium chloride.

The last sample so obtained was extracted with 50 cc. of hot, absolute alcohol to free it of sodium chloride, which was filtered off. The alcoholic extract was then evaporated to dryness *in vacuo* and the residue taken up in water. An excess of barium hydroxide was added at 50° C., and the precipitate was collected by centrifugation. The precipitate was washed with three portions of hot water and then resuspended in dilute sulfuric acid and the barium sulfate precipitate was discarded after the solution no longer gave a precipitate with sulfuric acid. The tannic acid was again precipitated with sodium chloride, dissolved in an equal mixture of hot alcohol and acetone and precipitated with ether. This precipitate was again suspended in water and the tannic acid was precipitated with sodium chloride. No determination of the salt content of the dry precipitate was made.

This cleaned product had the properties of tannic acid. It turned black with ferric chloride solution and precipitated egg albumen. It tanned the rats' abdominal wall which had been denuded of skin and caused necrosis of the superficial portion of the abdominal musculature just as strong tannic acid solution would do.

In 21 mice, subcutaneous injections of the cleaned material was followed regularly by hepatic necrosis when solutions of 1% or greater were given.

From these results it was concluded that the cleaned tannic acid had the same action in the experimental animal as the tannic acid (U. S. P.); and, furthermore, that the procedures used had in no way lessened the untoward action of tannic acid on the liver. Therefore, the necrotizing action of commercial tannic acid (U. S. P.) would seem to be due to tannic acid *per se*, and not to any contaminating material.

APPLICATION OF EXPERIMENTAL RESULTS TO THE TREATMENT OF HUMAN BURNS

The Local Necrotizing Effect.—The experiments in rats suggest that if tannic acid came in direct contact with undamaged human subcutaneous tissues or muscles some necrosis would result, and that if the stronger preparations of tannic acid, 20%, came into contact with undamaged muscle there would be necrosis to a depth of five to ten muscle fibers. Applied to the human

abdominal wall denuded of skin, the necrosis would not extend one-quarter of the distance through the muscle mass or a distance anywhere approaching this fraction as it did in the rat, because of the much greater thickness of the human abdominal muscle mass.

But it should be constantly borne in mind that the human third-degree burn is not simply an area denuded of skin, but is an area on the surface of which there is usually necrotic tissue caused by the burn. It may be that this necrotic tissue would prevent the underlying viable tissue from suffering the necrotizing action noted in the rat. The degree of ease with which tannic acid penetrates necrotic tissue is not known.

The local damaging effect of tannic acid would be of little consequence in deep burns because the loss of a few additional strands of tissue would not matter. The damaging effect might be of greater importance when remnants of hair follicles and epidermis were destroyed and might interfere with the regeneration of epithelium.[4] In a recent human burn of second-degree treated with tannic acid in 5% concentration, however, regeneration of epithelium was sufficiently rapid to indicate that the local necrotizing effect, if present at all, had no significance. (Personal observation, R. D. B.)

In brief, it might be argued that the only precautions to be observed, so far as the local lesions are concerned, is not to use high concentrations of tannic acid (15 or 20%); and to bear in mind the possible necrotizing action of the drug in those burns which are partially of second and partially of third-degree.

The Effect on the Liver.—The experimental data can not be applied directly to the human case of burns because it is not clear that the absorptive power of a burn is the same as that of a body surface denuded of skin. The evidence that tannic acid can be absorbed through a burned area rests on the observations made at autopsy upon human cases of burns and on experiments on dogs.[6]

These experiments on rats suggest that in human burns absorption of tannic acid might be expected from the ointment and from baths of the aqueous solutions to about the same extent, and that minor degrees of hepatic necrosis would be of brief duration, not permanently damaging, and of no consequence, while severe degrees of necrosis might be associated with a fatal outcome.

SUMMARY AND CONCLUSIONS

1. Experiments with rats and mice have corroborated experiments by others that death and hepatic necrosis can be produced by the subcutaneous injection of tannic acid.

2. Neutralized tannic acid of p_H 7.2 injected subcutaneously was as damaging to the liver as the tannic acid (U. S. P.) of p_H 3.

3. Gallic acid introduced subcutaneously produced no hepatic damage, indicating that it is not the gallic acid component of tannic acid which is responsible for the necrosis of the liver.

4. Hepatic necrosis was produced in rats by removing the ventral skin, immersing the rat in a tannic acid bath (15 minutes) and washing the treated area with tannic acid the following day. Minor hepatic necrosis occurred in some of the rats when one-fourth of the skin of the body was removed and solutions as low as 2.5% were applied. Severe hepatic necrosis was produced by 20% tannic acid applied to an area of the same size, and some of the rats which received this concentration died. In control experiments in which other rats were treated with water in the same manner, no hepatic damage was noted.

5. Tannic acid produced hepatic necrosis whether aqueous solutions or ointments were used.

6. Tannic acid of 10%, or less, sometimes produced necrosis of viable tissue over the denuded areas, and regularly when concentrations greater than 10% were employed.

7. A substance which turned black on the addition of ferric chloride was demonstrated in the urine of rats which had received tannic acid subcutaneously.

8. Direct application of these experimental results to the treatment of human burns with tannic acid should be made with extreme caution, especially those dealing with absorption from a skinned area, since absorption from burns has not been investigated in this study.

The authors wish to acknowledge the assistance of Mrs. Margery Prindle, M.A., in this study.

REFERENCES

1 Davidson, E. C.: Tannic Acid in the Treatment of Burns. Surg., Gynec. & Obst., **41**, 202, August, 1925.

2 Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment. Brit. J. Surg., **25**, 826, April, 1938.

3 Tenery, R. M.: Cutaneous Burns. Am. J. M. Sc., **203**, 293, February, 1942.

4 Taylor, Frederic: The Misuse of Tannic Acid. J. A. M. A., **106**, 1144, April, 1936.

5 Wells, D. B., Humphrey, H. D., and Coll, J. J.: Relation of Tannic Acid to the Liver Necrosis Occurring in Burns. New England J. Med., **226**, 629, April 16, 1942.

6 Editorial, J. A. M. A., **119**, 416, May 30, 1942.

7 Belt, T. H.: Liver Necrosis Following Burns; Simulating the Lesions of Yellow Fever. Jour. Path. & Bact., **48**, 493, May, 1939.

8 Buis, L. J., and Hartman, F. W.: Histopathology of the Liver Following Superficial Burns. Am. J. Clin. Path., **11**, 275, April, 1941.

9 Weiskotten, H. G.: Histopathology of Superficial Burns. J. A. M. A., **72**, 259, January 25, 1919.

10 Bardeen, C. R.: Study of the Visceral Changes in Extensive Superficial Burns. J. Exper. Med., **2**, 501, September, 1897.

11 Rost, E.: Über die Ausscheidung der Gerbsäure und einiger Gerbsäurepräparate aus dem thierischen Organismus. Theilweise nach Untersuchungen des Herrn Dr. H. Spickenboom. Arch. f. Exper. Path. u. Pharmakol., **38**, 346, February, 1897.

A CLINICAL TEST FOR DIFFERENTIATING SECOND FROM THIRD DEGREE BURNS*

JAMES A. DINGWALL, 3RD, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

IN THE PAST, decision as to whether a burn was second or third degree at the outset, has rested on gross inspection, its value being dependent on an individual's experience with large numbers of burns. There have been many instances, however, in which it was impossible to tell the true extent of the injury until considerable time had elapsed after the reception of the burn, and decision as to the ultimate treatment has had to be postponed.

The idea is receiving increasing acceptance that an excellent treatment for third degree burns, if not too extensive, is immediate excision of destroyed tissue, followed by grafting. Before undertaking this, however, one must accurately delimit those areas in which skin regeneration is possible, from those in which the entire cutis is destroyed both in order to take advantage of any remaining cells as foci of growth, and to eliminate as rapidly as possible the dead tissue so that granulations with subsequent scar tissue formation may be minimized.

It is the purpose of this communication to present a clinical method of distinguishing between burns of second and third degree, which is applicable shortly following injury.

METHOD.—Lange and Boyd,[1] and Herrlin, *et al.*,[2] have shown that sodium fluorescein injected intravenously may be employed to reveal "the presence and adequacy of the circulation," and have suggested its use in measuring the circulation time; determining the viability of the bowel in experimental and clinical cases of strangulated hernia; and in cases of gangrene of the extremity, where it is desired to demarcate satisfactory circulatory levels for amputation.

With this in mind, experimental animals (rabbits and dogs) were burned by means of a steam-heated hot plate applied to the shaved skin. Third degree burns were produced, as proved either by excision and examination of the involved area, or by subsequent sloughing and granulation. Immediately after burning, five to ten cubic centimeters of sodium fluorescein was administered, and the area viewed under ultraviolet light screened with a Wood filter. The burned areas appeared as sharply demarcated blue-black patches in contrast to the surrounding yellow-green color of normal fluorescein-containing skin. The next step was an attempt to produce milder burns. Since it is fairly well established that second degree burns comparable to those encountered in man may not be produced in the usual laboratory

* This study was carried out under a grant from the Wallace and Tiernan Products, Inc.

animal,* human volunteers† were given second degree burns which blistered, desquamated, and subsequently healed without granulation. Following each burn ten cubic centimeters of 20% sodium fluorescein was given intravenously, and the burned sites examined as above. In every instance the areas appeared yellow-green, generally more intense in color than the surrounding skin.

Finally, a similar test was performed in six patients who had suffered accidental burns. At the time of application of the test, it was desired to know whether both second and third degree burns were present, and, if so, to separate them. As in the experimental burns, third degree areas were black, while second degree burns were yellow-green in color; the two being readily distinguishable from one another. The accuracy of the delimitation by this method was subsequently proved after sufficient time had elapsed, by the natural demarcation. Kodachrome pictures were taken and the color contrast presented was readily apparent.

COMMENT.—In evaluating this test, the basic pathologic differences between second and third degree burns should be borne in mind, as well as their rôle in the production of the color contrasts. For simplicity, we consider a second degree burn to be one in which not all of the skin epithelium is destroyed, thus permitting regeneration if only from the cells of the hair follicles and sebaceous glands. A third degree burn embodies complete destruction of the epithelium, and postulates granulation. Fluorescein when administered intravenously diffuses throughout the vascular tree and, after a sufficient time, some of the drug undoubtedly enters the intercellular fluid and stains the cells. In normal skin, it permeates into all the minute vessels of the corium, even the subepithelial capillaries, and may be visualized on the surface. On the other hand, if enough tissue destruction has occurred, as in a third degree burn, vascular transportation of the drug to the upper and visible skin layers is impossible. However, in any one area, some vessels may be intact, while others are destroyed, and it is here that a mottling of color occurs suggestive of a deep second degree burn as opposed to the diffuse yellow of a more superficial injury. With some practice, one may easily appreciate this difference.

We have given no more than ten cubic centimeters of sodium fluorescein to any one patient, although more has been used in another clinic.[1] We have found that there is clinical evidence of its presence in the blood stream by visual skin discoloration for about 10–12 hours following administration, and that its presence in the urine is noted for about 30–40 hours. In our experience, it appears to be a safe drug for intravenous use in such dosage, the only untoward symptoms being a transient nausea if given too fast (three patients), and a questionable attack of renal colic in one hypochondriacal individual, which occurred two days following its administration, and was unaccompanied by objective urinary findings. We have noted no ill effects

* Save, in our experience, a suckling pig.

† Students of Cornell University Medical College.

from the accidental subcutaneous extravasation of the drug in animals or humans.

SUMMARY

A method of distinguishing second from third degree burns is introduced which has proven reasonably accurate in a small series of cases, and depends only on the recognition of sharply opposed color contrasts. It is hoped that its widespread application may aid in preventing some of the unfortunate end results of accidental burns, and may cut down appreciably the duration of hospitalization of such patients, making the initial prognosis more accurate.

REFERENCES

1 Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation. Med. Clin. North America, **26**, 943–952, May, 1942.

2 Herrlin, J. O., Jr., Glasser, S. T., and Lange, K.: New Methods of Determining the Viability of Bowel. Arch. Surgery, **45**, 785–791, November, 1942.

PILONIDAL SINUS

APPLICATION OF PLASTIC SURGICAL PRINCIPLES IN A NEW SURGICAL APPROACH

MAJOR GEORGE T. MCCUTCHEN, M.C.

STATION HOSPITAL

CAMP FORREST, TENN.

THE IMPORTANCE TO THE ARMY of the treatment of pilonidal cysts is very real, as may be inferred from the mass of literature being presented relative to them recently. The condition is usually considered a minor one, but the morbidity incident to a conventional radical excision, which obviates the likelihood of recurrence, is a major problem.

The embryology of pilonidal sinus has been studied by many investigators. Two tenable theories of origin have been evolved. The one bearing the bulk of substantiating evidence is that the sinus is derived from epithelial cells of the neural tube which fail to dissociate during prenatal life when other elements of the embryonal "tail" do so. The other theory is that the sinus is derived from an invagination of epidermal elements during embryonic life. Contention over these theories has entertained embryologists, but a settlement of the argument would not provide the clinical surgeon with a solution of his problems.

However, we do learn a great deal from the study of the pathology of the condition. First of all, and most important in the establishment of an operative approach, is the fact that the sinus is a disease of the subcutaneous fat and not a disease of the skin. There are usually, but not always, dimples of small size in the sacrococcygeal region, which form the only connection with the skin, except where artificial ones are made by surgical incision or spontaneous rupture of an abscess. These dimples and artificial openings have no surgical significance *per se*, but are important only if they connect with the epithelial-lined tract in the subcutaneous fat. This pathologic fact is emphasized because it is overlooked in most discussions of the subject, and because it makes it obvious that the removal of skin is unnecessary if the subcutaneous fat can be adequately exposed and resected without it. Second, it is impossible to determine the extent of the epithelial tract in a given case by any clinical test, be it injections of dyes, radiopaque substances, or the passage of a probe, because the tract may be occluded with pus and débris, or the lumen so small that it will not admit any of these materials. This fact makes it necessary to remove an adequate amount of fat surrounding the tract or recurrences will appear. Third, infection is almost invariably present in the tract which is causing symptoms. Primary closure fails so often because infection leads to fat necrosis which, in turn, leads to wound separation and the formation of dead space. This dead space is, in reality, another sinus, and must be treated by incision and packing. Provision for adequate drainage is a strong point on the side of radical excision with open

packing, but prolonged healing time makes this procedure undesirable. Fourth, is an anatomic feature of the region. The gluteal muscles exert a pull on the skin and subcutaneous fat which is a prime factor in the formation of dead space under an incision which has been subjected to primary closure. It will also cause a poor result in the so-called "partial primary" closures because the sutures maintaining the closure will cut through and allow the wound to gape. Restraint with adhesive, or other devices, is of no avail in preventing the dogged-tug of these muscles. A sound surgical approach should include a release from this lateral pull on the wound.

The number of methods suggested in the literature for the relief of this condition is legend, and would not bear enumeration, but the basic principles underlying approaches are not at great variance and should be a part of the armamentarium of anyone entrusted with the care of these patients. The basic features of suggested surgical approaches are as follows: (1) Radical excision, with open packing. (2) Radical excision, with immediate primary closure. (3) Radical excision, with closure by flaps detached from the adjacent area. (4) Radical excision, with partial primary closure. (5) Radical excision, with delayed partial primary closure. (6) Destruction of tract with sclerosing solutions or cautery. (7) Exteriorization of tract by incision and open packing with gauze. (8) Excision of tract with cautery or sharp dissection by undermining of wound edges, followed by partial primary closure.

Reference to the preceding paragraphs will suggest the advantages and disadvantages of these methods. We may emphasize that any method which falls short of radical excision is fraught with the likelihood of recurrence, and that primary closure after radical excision, with sacrifice of skin, is known to be treacherous because of the probability of wound separation.

All methods of radical excision so far suggested entail the sacrifice of skin primarily because it has been deemed impossible to provide adequate exposure of the underlying tract in the fat without this sacrifice. The method which we shall describe provides for this exposure by the undermining of four flaps, and a tract of any size can thus be exposed. It may be noted that this method is particularly applicable to the extensive tract in which sacrifice of a large amount of skin is customarily practiced. In the series reported, there have been a total of 49 cases. Ten cases had very small and superficial tracts which were treated by a method involving some type of partial primary closure and a method which we developed in the process of evolution of the more perfected procedure. Thirty-nine cases were treated by the method to be described. These facts suggest only that the large majority of cases fall into the extensive group and must be handled by radical methods.

In the 39 cases subjected to this method of treatment the average healing time was 38 days. The shortest healing time was 23 days, and the longest 61 days. Two cases returned about one month after discharge from the

hospital complaining of a draining site over the sacrum. In both cases one of the cotton mattress sutures had become imbedded under the skin. After removal of these sutures the wounds healed readily. This experience has led us to cut these sutures longer at the operating table so that they may be more readily identified at the scheduled time for their removal. Apology must be made for the fact that a long-term follow-up is not available in this series. However, we feel free to believe that the recurrence rate will not be any greater than that already established for other procedures entailing the radical removal of fat from the sacrococcygeal region. The first of these operations of the reported series was performed September 9, 1942.

TECHNIC OF OPERATIVE PROCEDURES

Adequate exposure of the fat containing the tract is provided by three incisions. Two sides of a triangle on each side of the natal cleft are made with the apex of these incisions about one inch from the midline. Each limb is made approximately one and one-half inches long. The apices of these partial triangles are joined across the midline by another incision. The incision is carried only through the skin. For subsequent use for traction on the flaps, sutures are placed on the edges of these incisions at strategic points. The lower flap is then undermined by sharp dissection to a point well below the coccyx. The flap is not stripped entirely of fat, but the under surface of the skin is so exposed that a tract running close to it could be easily discovered. The upper flap is undermined in the same manner to a point well above the upper border of the sacrum. One tract is illustrated which extended very high in this direction. More exposure of the underlying fat can always be provided by extending the limbs of the incomplete triangles on both sides either up or down, as the case may require. The lateral flaps are formed by the undermining of the incomplete triangles down to their bases. It will be noted that these flaps are designed so that they have very broad bases, which make sloughing of the tips unlikely. We have encountered very minor sloughing in only two cases. The extent of these sloughs was no larger than some of the stab wounds which we have purposely made and did not delay healing time.

Up to this point the tract in the fat has not been attacked, but it is now thoroughly exposed by retraction of the flaps and may be removed *en bloc*. No hard and fast rule can be set forth as to the amount of fat which should be removed, but it should be generous. Lack of exposure has been eliminated, and we have found that the small amount of fat left on the flaps will proliferate and provide a soft, pliable pad over the sacrum and coccyx in a very short time. Patients have not complained of pain and tenderness in this area upon return to their duties. The removal of the "block" containing the tract should be systematic, and should lay bare the medial aspects of the glutei as well as the fascia over the lower lumbar region, sacrum and coccyx. Rigid hemostasis is secured in the base of the wound and on the flaps. The wound is then thoroughly

FIG. 1

FIG. 2

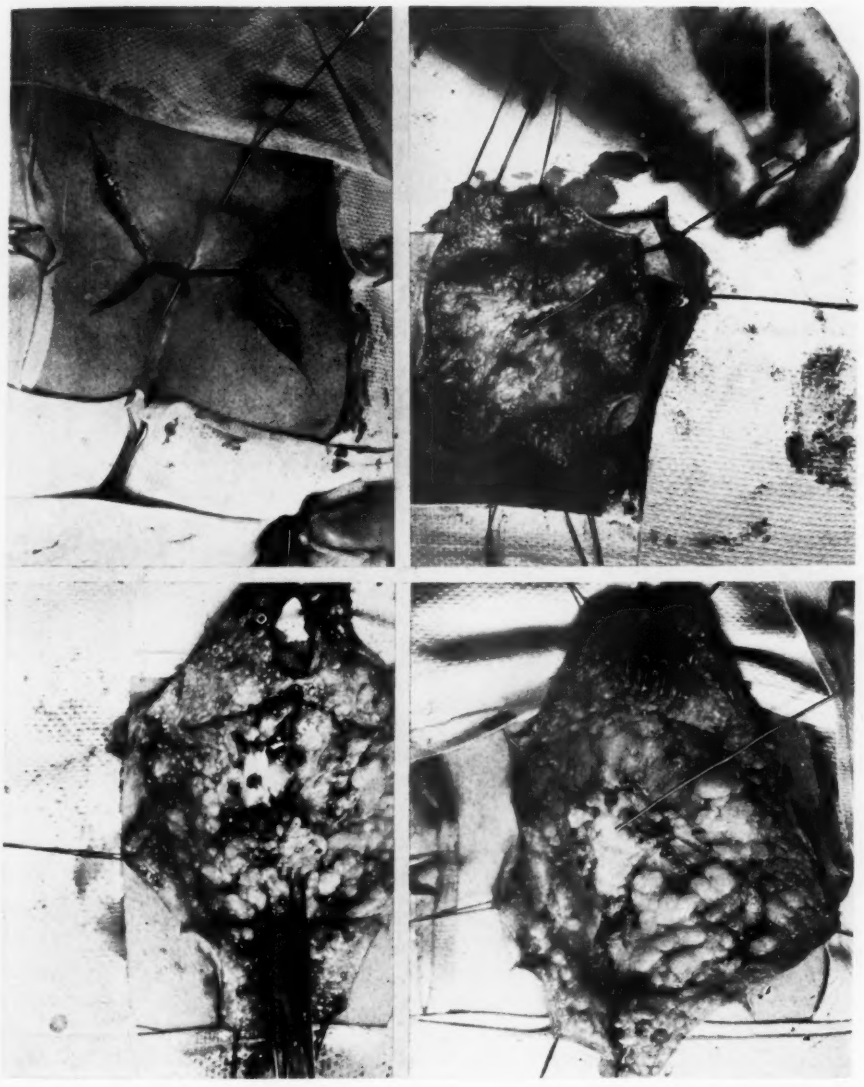


FIG. 3

FIG. 4

FIG. 1.—Primary Incisions: Probe is inserted into portion of tract, tract also extended downward toward coccyx but would not admit probe. This is true of a great many tracts and serves to emphasize the inadequacy of the probe in determining the limit of excision.

FIG. 2.—Flaps have been dissected free. Tract is exposed and ready for removal. Probe still lies over part of tract which will admit it.

FIG. 3.—The fat is being removed *en bloc*, with the aid of traction. The surface of the sacrum and medial aspects of the glutei are exposed.

FIG. 4.—A block of fat over the sacrum and coccyx have been removed. A very small amount of fat has been left on the flaps.

bathed with warm normal saline solution in large amounts. By retracting upward on the flaps a large cup can be made of the wound and the solution poured in. Any bleeding produced by this bathing should be rigidly controlled. Any tabs of fat which float and are loosely attached should be débrided. This cleansing and débridement and attention to hemostasis all contribute to the production of a clean postoperative wound. Five Gm. of sulfanilamide powder are then sprinkled into the wound with a salt shaker. Stab wounds are made in all flaps according to the pattern shown in the illustrations. These provide drainage for a potentially, or actually, infected wound. They would also serve to make the flaps longer if this were necessary, but it will be found that the flaps fall into their original positions without the slightest tension in any direction. In fact, one frequently finds more tissue than he needs and is able to débride the dimple site. This may be done in every case if desired. Points where spontaneous rupture of an abscess has occurred remote from the dimple site, may be removed by making a stab wound involving this area. The central flaps which cover the sacrum and coccyx are free of lateral pull by the glutei, and dead space will not be created by lifting of the flaps. The flaps are secured in position by mattress sutures placed at strategic points. These sutures are passed through the skin, then engage the underlying bed of the wound securely, then pass back through the skin and are tied. No sutures are placed in the edges of the wounds to provide apposition of the incisions. The incisions fall together naturally when the flaps are replaced. Close apposition is not desirable because of the potential danger of infection. When the mattress sutures are placed a row of them is left long on each side about three-quarters of an inch from the midline. These are tied across a gauze roll, about two inches in diameter and about four inches long, which lies in the natal cleft and maintains pressure on the central portions of the flaps. This gauze roll is impregnated with glycerin, which preserves the soft consistency of the pack and prevents it from becoming malodorous as it accumulates secretion from the wound. A pressure dressing of cotton waste is then applied. This top dressing is changed as necessary, but the gauze roll is left in place for approximately one week. Since it is held in place with sutures no amount of movement, straining at stool, or other activity can dislodge it. The mattress sutures are left in place from 10–12 days. Patients are allowed food as soon as it is tolerated, and no attempt is made to restrain bowel movements. Sitz baths are begun after the tenth day and continued until healing is complete. The patients are able to go to the bathroom as soon as they have recovered from the spinal anesthesia, and are allowed freedom of movement after the third postoperative day. An adjunct to treatment is the administration of the sulfonamides by mouth before and after operation as well as applying it directly to the wound. We have not used this adjunct universally. Gross infection has appeared in a large percentage of our wounds, but the presence of multiple stabs in the flaps has provided adequate drainage, and floating of the flaps has not

FIG. 5

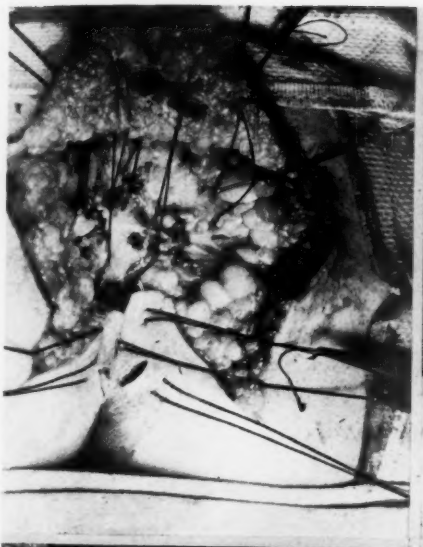


FIG. 6

FIG. 7

FIG. 8

FIG. 5.—Stab wounds have been created in the flaps. The wound has been thoroughly cleansed by irrigation with saline. The floating fat is débrided. Bleeding caused by the irrigation is rigidly controlled. Sulfanilamide is sprinkled in the wound. Mattress sutures are placed at strategic points on the flaps. The probe is pointing toward the suture as it engages the fascia over the sacrum deeply. The sutures on the inferior flap have been drawn taut to demonstrate the replacement accomplished.

FIG. 6.—Replacement of flaps has been accomplished. Sutures have been left long in a row alongside the natal cleft. These will be used to hold the dressing in place. The original incisions fall together naturally, but sutures are placed in them to prevent overlapping.

FIG. 7.—A gauze roll impregnated with glycerin has been placed in the natal cleft and secured with the sutures which were left long. A further pad of cotton waste is placed over this dressing and held in place with adhesive tape. The latter can be changed whenever it becomes soiled. The former is left in place from seven to eight days.

FIG. 8.—The Healed Wound. The skin becomes resilient and freely movable over the sacrum and coccyx.

occurred. Infection has not deterred healing as far as we have been able to determine. We expect infection and provide for it.

During the evolution of this technic two other flap type operations were tried and found to be inadequate. The first was a T-shaped incision with the short limb of the T about one and one-half inches from, and

Fig. 9.—The tract has been laid open and outlined with cotton thread. A generous amount of fat has been removed around it.

parallel to, the midline. The long limb of the T extended across the midline near the midsacral region. The undermining of flaps was found to provide inadequate exposure for the extensive case, and the tendency for flaps to "rise" was great because of inadequate release of lateral tug by the glutei. The second was the making of another lateral incision at the base of the long oblique limb of the T. This provided two lateral incisions which were staggered, that is, at different levels on the two sides of the transverse wound. Undermining provided adequate exposure but a tendency to floating of the flaps was again encountered. Adequate disposition had not been made of the tugging glutei.

One incident should be mentioned in order to avoid a repetition of it. A long coccyx whose tip was curved posteriorly was encountered in one case. This protruding tip was not removed. At the first dressing it was found presenting itself through a stab wound. It was necessary to remove this protruding tip at a later date. It would have been much better to have removed it at the operating table, although healing was not impaired because of failure to do so.

We believe that the procedure, as it was finally evolved, attacks the basic problems presented by the pathology of this troublesome condition. Adequate exposure is provided so that the tract can be removed in a radical manner. Unnecessary sacrifice of skin is eliminated without jeopardizing the extent of excision. The unfavorable effects of infection are eliminated by the provision for adequate drainage through stab wounds. The lateral tug of the glutei on the flaps is eliminated by the incisions made on each side during the formation of the flaps.

CONCLUSIONS

(1) Radical and extensive removal of the subcutaneous fat of the sacrococcygeal region is essential to the cure of pilonidal sinus without the likelihood of recurrence.

(2) A procedure making use of basic plastic and general surgical principles is presented, which eliminates the sacrifice of skin and still provides adequate exposure of the fat which should be excised.

(3) Healing time has been consistently short for a radical excision of the cyst.

(4) Hope is expressed that others will see fit to try this procedure while the present mobilization of young men in the army provides such a rich opportunity for the continuous and consecutive observation of a large group of cases.

REFERENCES

1 Buie, Luis A.: Practical Proctology. W. B. Saunders, Co. 1938. Page 477.

2 Cutler, C. C., and Zollinger, Robert: Sclerosing Solutions in the Treatment of Cysts and Fistulae. Am. Jour. Surg., **19**, 411–418, March, 1933.

3 Gage, Mims: Pilonidal Sinus: An Explanation of Its Embryonic Development. Arch. Surg., **31**, 175–180, August, 1935.

4 Rogers, Horatio, and Hall, M. G.: Pilonidal Sinus: Surgical Treatment and Pathological Structure. Arch. Surg., **31**, 742–766, November, 1935.

5 Colp, R.: Treatment of Pilonidal Cysts and Fistulae. Surg. Clin. North America, **9**, 695, 1929.

6 DePrizio, Carl J.: Pilonidal Cyst and New Improved Type Operation. The Military Surgeon, **91**, 292–298, 1942.

7 MacFee, Wm. F.: Pilonidal Cysts and Sinuses: A Method of Wound Closure. ANNALS OF SURGERY, **116**, 687–699, November, 1942.

8 Dunphy, J. E., and Matson, D. D.: The Treatment of Pilonidal Sinus. Surg., Gynec. & Obstet., **75**, 737–742, December, 1942.

9 Sanders, Robert L.: Secondary Closure of Pilonidal Sinus Wounds. Hudson, Richard T. Discussion of Paper. South. Med. Jour., November, 1941.

10 Poth, Edgar J.: A Technique of Skin Grafting. Surg., Gynec. & Obstet., **75**, 779–784, December, 1942.

11 Levy, Edward: Personal communication.

SYNOVIAL CYSTS OF THE POPLITEAL SPACE: CLINICAL SIGNIFICANCE AND TREATMENT

G. E. HAGGART, M.D.
BOSTON, MASS.

FROM THE DEPARTMENT OF BONE AND JOINT SURGERY, THE LAHEY CLINIC, BOSTON, MASS.

THE PURPOSE of this paper is (1) to record further clinical experience with synovial cysts of the popliteal space; (2) to emphasize that these cysts often cause symptoms which suggest internal derangement of the knee joint and that unless the popliteal space is carefully examined the presence of such a cyst may well be missed; and (3) to point out that excision of the cyst relieves symptoms and results in excellent function of the knee joint.

In a previous paper[1] the literature on this subject was reviewed, as well as the origin of the eponym, "Baker's cyst," frequently employed to describe synovial cysts of the popliteal space.

ETIOLOGY

Synovial cysts of the popliteal space are due to a posterior herniation of the knee joint capsule or to hyperplasia—"fluid distention"—of one of the adjacent bursae, most frequently the semimembranosus bursa. In my experience, herniation of the joint capsule has been the most frequent cause for the condition. Wilson, Eyre-Brook and Francis[2] consistently found that the cyst was on the medial side of the popliteal space, originating from, or a part of, the semimembranosus bursa. Therefore, they concluded that the synovial sac is a congenital deviation of the normal structure.

Of those patients shown at operation to have true posterior herniation of the knee joint capsule, the majority give a definite history of trauma, particularly of a sudden, forcible hyperextension of the knee joint. The propensity of patients to ascribe a condition to some injury is well known. But the type of trauma described, that of hyperextension of the knee, is not so frequently encountered. In this group of cases, such an injury seemed to be of real significance as a causative factor in the development of the herniation.

On the other hand, of those patients known to have an hyperplastic bursa as the cause of the synovial cyst, a history of trauma was obtained in 75 per cent. However, in no single instance was it a type of injury that resulted in forceful hyperextension of the knee.

Upon operation, four children, in the age group of 5 to 12 years, exhibited enlarged semimembranosus bursae, which bears out the point made by Wilson, *et al.*,[2] namely, that one would not expect a hernial protrusion in a joint capsule in a child. One of these cysts was recurrent, the child having been operated upon twice elsewhere. In this patient, who gave a definite history of recurrent swelling of the knee, a large communication with the knee joint capsule was demonstrated.

PATHOLOGY

The histologic examination of the lining membrane of the synovial sac, whether it was a hernial protrusion or an enlarged bursa, revealed a true mesothelium similar to the synovial membrane of the knee joint. Acute and chronic inflammation of the serosa was evident, together with moderate to marked round cell infiltration of the subserous layers. In the case of posterior herniation, the outer wall of the sac, especially that immediately

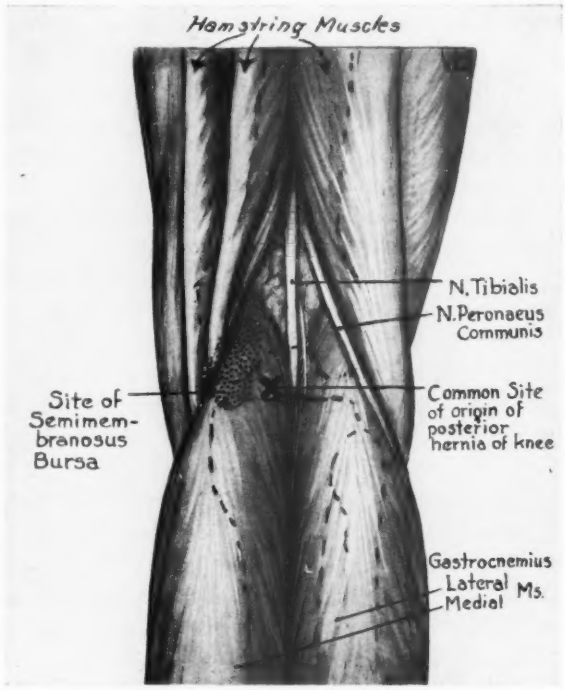


FIG. 1.—Both the semimembranosus bursa and the usual site of origin of posterior herniation of the knee joint are located beneath the medial head of the gastrocnemius muscle. A large synovial cyst from either source will fill the popliteal space and, as described, extend down the lower leg.

adjacent to the site of origin, was composed of relatively dense, fibrous tissue similar to the capsule of the knee joint, while the more distal portion of the sac was composed of fine connective tissue, quite friable and easily torn. This distal part of the sac was always firmly adherent to the adjacent fibers of the gastrocnemius muscle, especially the medial head. In patients shown to have a true posterior herniation there was a communication between the cyst and the knee joint. Of this group, 60 per cent gave a definite history of intermittent swelling of the knee, and presented a picture strongly suggestive of internal derangement of the articulation. Of those patients found to have a distended bursa as a cause of the synovial cyst, 20 per cent reported intermittent swelling of the knee, and in each instance in this group a communication with the knee joint was established at operation.

CLINICAL FINDINGS—INCLUDING ROENTGENOLOGIC EXAMINATION

Patients with synovial cysts of the popliteal space most frequently request medical advice because of aching discomfort in the knee, often associated with recurrent swelling of the joint. All the patients with relatively large cysts also had noted intermittent swelling of the lower leg and ankle region, particularly evident after standing for a long period of time. The longest duration of symptoms was six years, and this particular patient reported intermittent swelling in the popliteal space and at times in the knee joint itself for an interval of four years before operation. From four patients who had noted the swelling in the popliteal space, as well as intermittent effusion in the joint, a detailed history revealed that appearance of fluid in the knee coincided with sudden diminution in swelling in the popliteal space. The general character of the symptoms was indicative of an internal derangement of the knee joint.

On clinical examination these synovial cysts present themselves as a cystic swelling, the major part of which is distal to the transverse flexion crease of the popliteal space. The swelling has a definite elastic sensation of contained fluid, and in a typical case, with the knee flexed, a ball-like cystic mass in the popliteal fossa can be demonstrated.

Except in obese patients, these cysts are visible on inspecting the popliteal space when the extremity is placed in the position of hyperextension of the knee joint. Swelling due to an enlarged semimembranosus bursa is more obvious on the medial side of the popliteal space, while that due to a posterior herniation is found at or near the mid line (Fig. 1).

The usual routine examination of the knee rarely exhibits any tenderness along the joint line and, as noted, there may or may not be increased fluid within the knee joint. Instability of the joint was not encountered.

In this group of cases the roentgenograms of the knee region consistently were negative, except in older patients in whom there was some degree of degenerative arthritis.

No attempt was made to inject air or oxygen into the cysts. Past experience with arthrograms revealed that this procedure created an appreciable irritation of the synovial tissue, and since surgery offers the one measure for cure of these cysts, such studies did not seem indicated. No attempt was made to aspirate the cysts, because in the majority of cases the thick contents would have necessitated the use of a large needle. Furthermore, as the cysts are multilocular, one would not expect to secure all the contents by aspiration.

OPERATIVE TECHNIC

After the first two cases, the remainder of the patients in this group were operated upon through a midline incision over the popliteal space (Fig. 2), because it was not possible to foretell accurately the extent to which the synovial cyst had extended down the leg. In six patients, for example, the distal tip of the sac was well below the midcalf region.

Therefore, an incision in the midline made the dissection much easier and more direct. With one exception, there was no keloid formation in the scars. In that instance an infection of the superficial layers of the wound developed as the result of a thrombophlebitis which began in the lower leg and progressively advanced up the extremity until it reached the popliteal region, when the superficial portion of the wound became infected and had to be packed open. A tourniquet is not employed as bleeding is comparatively minimal.

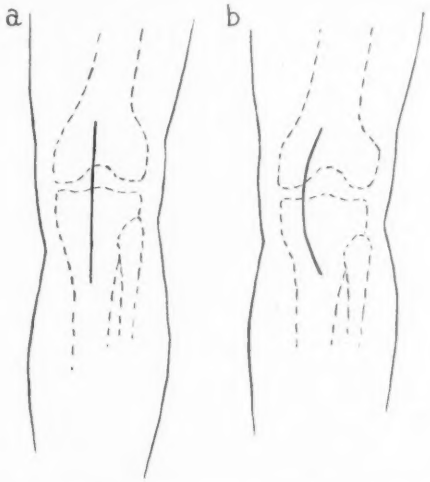


FIG. 2.—Diagram of types of incision: (a) As the operation is now carried out. (b) As performed in the early cases.

The deep fascia is incised in line with the skin, and with blunt dissection in the popliteal space, the underlying cyst comes into view. Then the incision is lengthened according to the extent of the cyst. The cyst wall is firmly adherent to the underlying tendon of the gastrocnemius muscle. Dissection begins in the distal part of the incision, and freeing of this cyst necessitates cutting away some of the tendon fibers, thus gradually progressing toward the midpopliteal region.

In a posterior herniation, the sac often exhibits a short, thick neck as the communicating channel between the cyst cavity and the knee joint. This is carefully defined, clamped, cut, and if sufficient tissue is present, the stump is inverted, and the aperture then closed with interrupted silk sutures.

When a communication with the knee joint is demonstrated, every effort should be made to close this opening. In some instances, particularly with hyperplastic bursae, this is difficult as the opening into the joint may vary from one to three centimeters in diameter, with relatively rigid walls. In such a case, fibers from the adjacent tendon are cut for suture material, or fascia lata is employed to close the defect. I believe that the care exercised in closing this aperture into the knee joint accounts for the fact that

no definite recurrence has been observed. In one patient the cyst may have recurred, but he has insufficient symptoms to submit to reoperation.

The concluding step in the operation, just before the cyst is actually removed, is to open it widely and carefully examine the inner wall, to determine, if not already known, the point of origin and whether the cyst communicates with the knee joint. The inner surface of the cyst presents numerous ridges and multilocular compartments, all of which should be

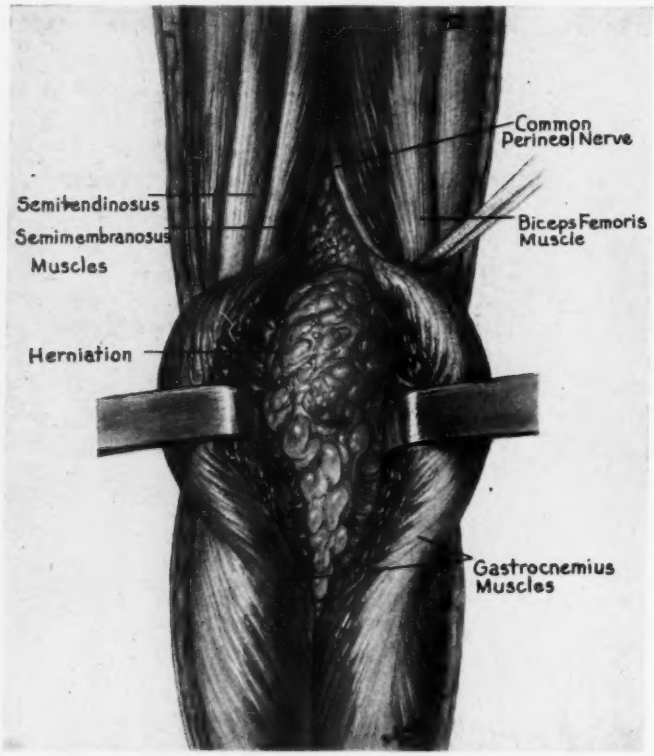


FIG. 3.—Synovial cysts of the popliteal space due to posterior herniation of the knee joint: To obtain this degree of exposure, it is necessary to cut away many of the tendon fibers from the gastrocnemius muscle. The cystic, friable distal portion of the cyst is well shown. The part outlined and not yet exposed is, as a rule, a fibrous band, always firmly attached to the gastrocnemius muscle.

investigated, because in three cases of enlarged semimembranosus bursa there were two separate openings into the knee joint. Hemostasis having been completed, it is important to resuture the deep fascia accurately.

Following closure of the wound, the patient is moved from the prone position, in which he was operated upon, to the supine position, and a plaster encasement applied from the high thigh to the ankle, with the knee in full extension. This encasement is left on for ten days, the objective being to obtain early healing of the wound with the joint in full extension. Furthermore, this position aids in preventing undue oozing. Thirty-six hours

after operation the patient is strongly urged to start active contraction of the quadriceps muscle, which he continues during the convalescent period.

In every patient in whom a definite communication between the synovial cyst and the knee joint was demonstrated, there was an appreciable post-operative effusion into the knee joint. In consequence, the convalescence and return to normal function in the early cases operated upon was delayed because of inability to overcome flexion of the knee. With the use of the

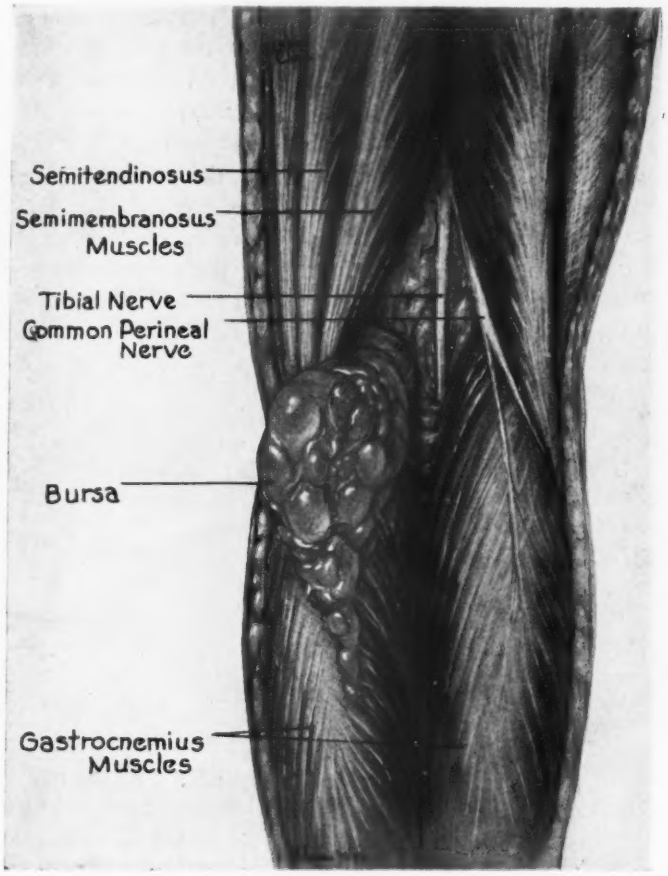


FIG. 4.—Synovial cysts of the popliteal space due to hyperplasia of the semimembranosus bursa: Note that the character of the cyst wall is similar to that shown in Figure 3.

plaster encasement, the knee in full extension, this discomfort was greatly alleviated, the degree of swelling in the joint was less pronounced, while the return of normal muscle function in the extremity was not delayed because of the active exercises instituted, namely, repeated contraction of the quadriceps muscle, and also lifting the extremity clear of the bed when lying supine. Following removal of the splint, progressively more active muscular exercises are encouraged, and the patient is then allowed up and progressive

weight-bearing is instituted. In the case of older patients, or those with relatively poor muscles, initial weight-bearing is carried out with the aid of crutches, and these are also employed when the patient has had a considerable operative reaction in the knee joint. The average period of hospitalization is 18 days.

RESULTS

Thirty-four patients with synovial cysts of the popliteal space have been operated upon. In one instance the cyst was bilateral, making a total of 35 cysts explored and removed. In 22 cases the cyst was the result of posterior herniation of the knee joint, while in the remaining 13 the cyst was due to enlargement and distention of the semimembranosus bursa. With the exception of one patient, there are no recurrences. This man now exhibits, three years after operation, a fullness in the popliteal space but in no sense a round, ball-like mass such as was present before surgery. He has refused reoperation because the knee does not bother him enough to warrant it. All patients in this series exhibit the same range of motion as was present before operation and have returned to their previous occupations. Swelling of the knee or lower leg region is absent.

REFERENCES

[1] Haggart, G. E.: Posterior Hernia of the Knee Joint: A Cause of Internal Derangement of the Knee. J. Bone & Joint Surg., **20**, 263–373, April, 1938.

[2] Wilson, P. D., Eyre-Brook, A. L., and Francis, J. D.: A Clinical and Anatomical Study of the Semimembranosus Bursa in Relation to Poplitéal Cysts. J. Bone & Joint Surg., **20**, 963–984, October, 1938.

HEMANGIO-ENDOTHELIOMA: A TUMOR OF BLOOD VESSELS FEATURING VASCULAR ENDOTHELIAL CELLS

ARTHUR PURDY STOUT, M.D.
NEW YORK, N. Y.

FROM THE SURGICAL PATHOLOGY LABORATORY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK, N. Y.

ACCORDING to Shaw (1928), blood vessels are formed in the embryo from angioblastic endothelial cells developing in the vascular layer of the mesenchyme. These cells first form solid cords and islands; lumens then appear in them and, finally, the isolated structures unite to form continuous tubes. If some of these structures fail to unite and remain segregated, they may grow independently and form hemangiomas which may subsequently unite with normal blood vessels or remain separated from them. They may remain as simple capillary tubes consisting of endothelial lining cells surrounded by a delicate reticulin framework or have, in addition, other cells normally associated with blood vessels, such as smooth muscle cells and pericytes, and also, on occasion, other tissues such as fat, smooth muscle, myxomatous tissue, bone, mature and immature red and white blood cells and perhaps other cells which may be derived from mesenchyme.

This accounts for the focal origin of a large majority of vascular tumors but it does not account for all, nor does it explain the spread and infiltrative growth of any of these tumors after they have once formed. This takes place by a process similar to the formation of capillaries in granulation tissue which occurs by the sprouting of endothelial cells from preexisting capillaries forming first a solid cord which secondarily becomes canalized. It seems probable that the malignant tumors in this series, which appeared in traumatized areas (Cases 8 and 14), must have developed in this fashion from the capillaries of granulation tissue. Probably all of the malignant tumors exhibit this type of growth in their infiltrative growth.

These methods of development make possible a very wide variety of gross and microscopic forms which have been endlessly described and named by pathologists, dermatologists, neurologists, and many others. It often leads to the formation of multiple tumors. Usually such tumors, even if they appear successively and grow to a large size, are not suspected of being malignant growths, but a few cases have been recorded whose behavior has raised this question. In some, such as the cases of Gloggengiesser (1939), Rabson (1938), Weiss (1911) in humans, and Sal (1931) in chickens, growth of vascular and related tissues occurred in widespread areas, as if it were due to a profound and perhaps systemic disturbance of the vascular system akin to von Recklinghausen's disease in the nervous system. If Kaposi's disease is neoplastic, it probably belongs to this group. In another group of cases, what have been described as benign hemangiomas have developed in one area

with the subsequent appearance of hemangiomas or hemangio-endotheliomas in other areas, as if they were metastases. This phenomenon has given rise to the term benign metastasizing hemangioma. The writer has never observed such an anomaly in his own material, and questions its occurrence. The subject will be discussed later in this paper.

In spite of the fact that blood vessels are ubiquitous, and benign vascular tumors exceedingly common, malignant tumors of blood vessels are exceedingly rare. Just how many of them have been recorded is impossible to say because many tumors have been reported as such with insufficient or obviously erroneous data. After reading reports of 118 cases labelled with some name suggestive of a malignant vascular tumor, the writer felt compelled to reject 41, or 35 per cent of them, either because there was an inadequate or no histologic report, or because, in his opinion, the illustrations and text described a tumor of some other kind.

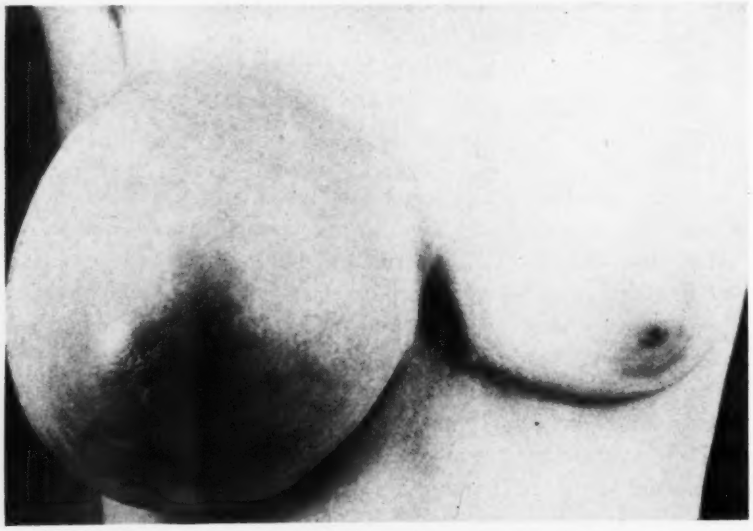


FIG. 1.—Case 1: Hemangio-endothelioma of the mammary gland in a 19-year-old girl, 14 months after onset, just before it was removed. The enormously enlarged bluish, turgid right breast weighed 1647 Gm., and contained a liter of blood.

There are certainly two, and probably three, malignant vascular tumors all characterized by the formation of vascular tubes but with different cells playing a dominant rôle in tumor growth. Attention has already been called to the group featuring the pericyte (Murray and Stout, 1942; Stout and Murray, 1942) for which the name hemangiopericytoma has been suggested. This group includes the glomus tumors, and the vast majority of them are benign. However, two cases have shown aggressive infiltrative growth, and at least one other is known to have metastasized—establishing the existence of a malignant variant.

Since smooth muscle forms an important part of many blood vessels, one might expect to find a vascular form of leiomyosarcoma. There is a benign

vascular leiomyoma (Stout, 1937, 1938), hence from the theoretical viewpoint, there is no reason why there should not also be a malignant form of this tumor. The evidence that such a neoplastic type exists is scanty. Fourmestraux and Foulon (1930), Grandclaude, Lambert and Driessens (1933), Leuret *et al.* (1930), and König (1921), believe that such tumors occur. The case reported by Leuret, and his associates, seems to have been composed of both atypical smooth muscle and many vessels, sometimes with heaped-up irregular endothelia and may, indeed, be truly compounded of both of these elements. It would be preferable to obtain further confirmation from others before accepting this as a definite type and not just a sport. This writer has not encountered such a tumor.

The third group is much better known and contains the majority of the malignant vascular tumors. It also forms vascular tubes but the important cell responsible for its aggressive growth and metastases is the endothelial cell. Because of this, it is best called by the name hemangio-endothelioma, devised by Mallory (1908), which is properly descriptive and has the added advantage of familiarity.

The writer has had the good fortune of assembling 18 such tumors from various sources, which he is permitted to present in a group through the generosity of several different pathologists and surgeons. Such a collection affords a better opportunity to study the characteristics and peculiarities of this tumor type than can be gained by attempting to analyze and collate the literature, for the reasons already indicated. The writer will base most of his remarks upon this material and only supplement it when necessary from the reports of others.

Eleven of the patients here reported were females and seven males. Three of them were colored. The age at onset varied from birth to 66 years; nine were less than 30 years of age but six were over 50 years. A tumor of the popliteal space (Case 14) and the one in the erector spinae muscles (Case 8) developed in traumatized areas.

The distribution of the primary lesions is shown in Table I.

TABLE I

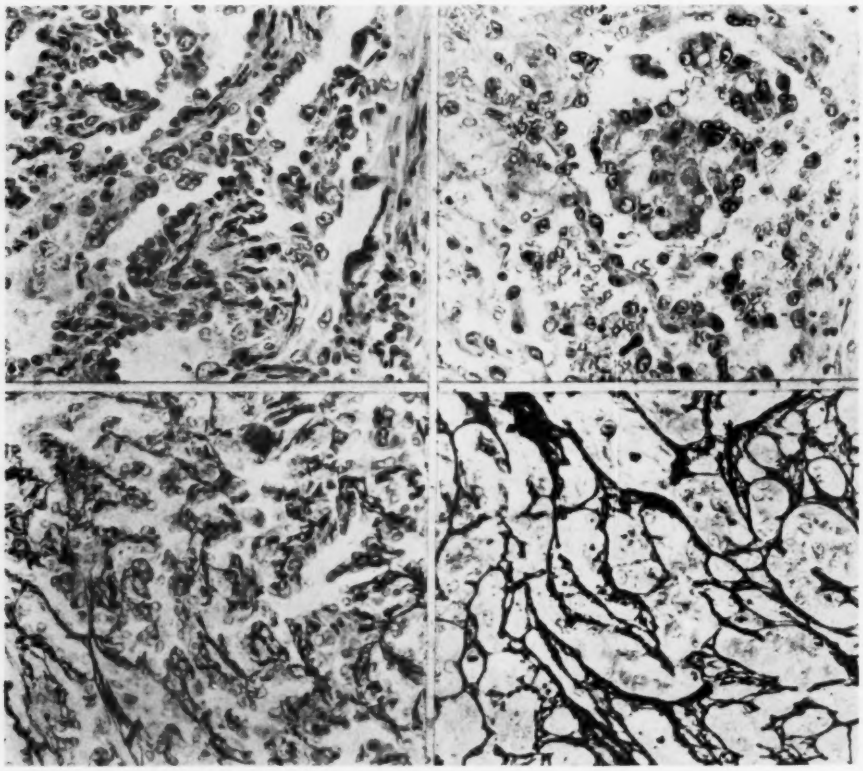
PRIMARY SITES OF HEMANGIO-ENDOTHELIOMAS

Mammary gland	3	Pleura	1		
Liver	2	Uterus	1	Skin and subcutaneous tissues	6
Bones	2	Orbit	1		
Striated muscles	2				

The majority of reported cases have been in the spleen, the liver, the bones, or in the skin and subcutaneous tissues. In acceptable reports of others can be found the following additional primary sites mentioned: Tonsil (de Bary, 1935); stomach (Sherrill and Graves, 1915); intestine (Magnusson, 1934); omentum (Ransom and Samson, 1934); retroperitoneal space (Beitzke, 1932; Leubner, 1935; Cannata, 1931); lung (Hall, 1935; Plaut, 1930); mediastinum (Shennan, 1914); heart (Gross and Englehart, 1937; Hewer and Kemp, 1936); pericardium (Scheidegger, 1937); ovary (Sovak

and Carabba, 1931); corpora cavernosa (Foulds and Flett, 1938); central nervous system (Turner and Kernohan, 1941).

The malignant nature of these tumors is fully confirmed by the outcome of the cases in this group. Of the 18 patients, ten are known to have died with metastases; one was last seen with local persistence of disease; one had had nine operations for local reappearances and was not followed after the



A B

FIG. 2.—Case 13: A (left). Hemangio-endothelioma of supraclavicular region. Anastomosing vascular channels lined by heaped-up, rounded atypical endothelia. Silver reticulin stain below outlines the vascular tubes.

Case 14: B (right). Hemangio-endothelioma of popliteal region. Poorly defined vascular channels lined by swollen polygonal endothelia are shown above, while below the silver reticulin stain accentuates the vessels by blackening their supportive framework (see Fig. 9). (×525 reduced)

last operation; three patients are without evidence of tumor 8, 12, and 30 months after removal; two were not followed; and only one is known to be well five years and two months after excision of a popliteal tumor.

As in other malignant tumors, the course of the disease is sometimes fulminating, as shown by Case 2, the 65-year-old woman, who was dead eight weeks after she first noticed a growth in her breast; and sometimes exceedingly protracted, as exemplified by Case 16, who during the first 19 years of her life had had a persistently growing tumor of the upper eyelid which constantly recurred in spite of eight attempts to remove it (Figs. 10 and 5 B).

The vascular nature of these tumors can generally be appreciated when one approaches them, and they have a tendency to bleed either into themselves or externally if they penetrate through a body surface. An example of the former condition is furnished by Case 1, the 19-year-old girl, with a tumor in the mammary gland which contained a liter of blood in it (Fig. 1). This bleeding was associated not only with a severe anemia but a purpura, with platelets averaging only 51,000. An example of surface bleeding is furnished by the uterine tumor (Case 10) which bled with increasing severity over a two-year period. On the other hand, Case 18 gave no evidence of its vascular composition even when excised, and only microscopic examination revealed its true nature. It developed in the eyebrow of a three-months-old boy, and was mistaken for a dermoid cyst.

Great vascularity and hemorrhages, while they may suggest a tumor of blood vessels, are not in themselves sufficient to prove that a neoplasm is indeed a malignant tumor of vascular elements. Both Molotkoff, (1933) and Ogilvie and MacKenzie (1936), have pointed out that chorio-epithelioma can be confused with blood vessel tumors and every experienced pathologist will recall extremely vascular hemorrhagic malignant tumors of other types. The diagnosis must, therefore, rest upon the histologic characteristics. These display themselves in a variable fashion and require presentation in some detail.

There are two features of the growth of hemangio-endothelioma which are striking and uniformly present in all true tumors of this kind, although they are sometimes masked and require differential staining clearly to demonstrate them. These are: First, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane; and, second, the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose. No tumor should be considered a hemangio-endothelioma unless these criteria are both present. The variations found are due to the marked variability in the number, shape, size and tinctorial peculiarities of the malignant endothelia. They may be irregularly rounded or polygonal (Figs. 2 A and B), or they may maintain an elongated shape (Figs. 3 and 4); they may form only a single continuous layer (Figs. 3 B and C), or they may become heaped up and more or less fill the lumen (Fig. 5 A). Usually they remain within the vascular tubes but occasionally they grow outside of it and form solid sheets of cells (Figs. 4 A and B). Whatever their shape, the tumor cells always differ from the endothelial cells of simple benign angiomas and normal blood vessels, although occasionally the blood vessels which are formed in the process of organization of a thrombus may simulate their appearance. It is usually easy to perceive that a tumor is composed of vascular tubes which tend to anastomose and are lined by atypical endothelia. When there is doubt about these things with ordinary stains, the relationships can be clarified by the use of a silver reticulin stain. This will cause the tubes

to stand out in sharp relief because each one, even in the most malignant tumor, has a delicate fibrous supporting framework and the silver brings out a distinctive pattern (Figs. 2, 3, 4 and 5). This pattern will be revealed with silver even when, with other stains, it is entirely obscured by an overgrowth of cells (Fig. 4 B). When ordinary stains make it impossible to decide

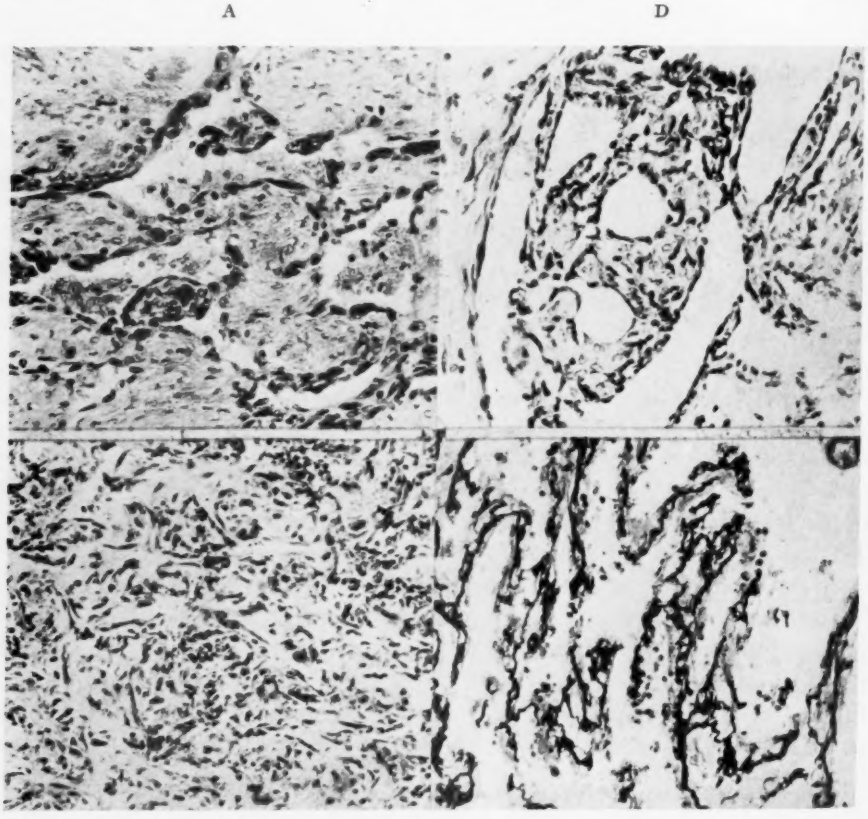


FIG. 3.—Case 10: A (upper left). Hemangio-endothelioma of uterus. Infiltrative extension of anastomosing blood vessels lined with bizarre elongated endothelia through the myometrium.
Case 6: B (lower left). Hemangio-endothelioma of tibia. Proliferation of anastomosing capillaries lined with hyperchromatic endothelia in the marrow.
Case 3: C (right). Hemangio-endothelioma of breast. Complex formation of vascular channels lined with hyperchromatic endothelia. The Laidlaw silver reticulin stain shown below accentuates the vascular pattern. (× 525 reduced)

whether cells are grouped inside or outside of a vessel wall, and so to determine whether one is dealing with endothelia or pericytes, silver staining of the vascular reticulin sheath shows the exact relationship of the cells beyond peradventure (Fig. 5 A).

If one tries to group these tumors in order to give them descriptive subtitles, one encounters almost insuperable difficulties, for the cellular appearance and make-up not only may vary in different parts of the same tumor but also in its recurrent or metastatic manifestations. Some features, however, deserve special emphasis.

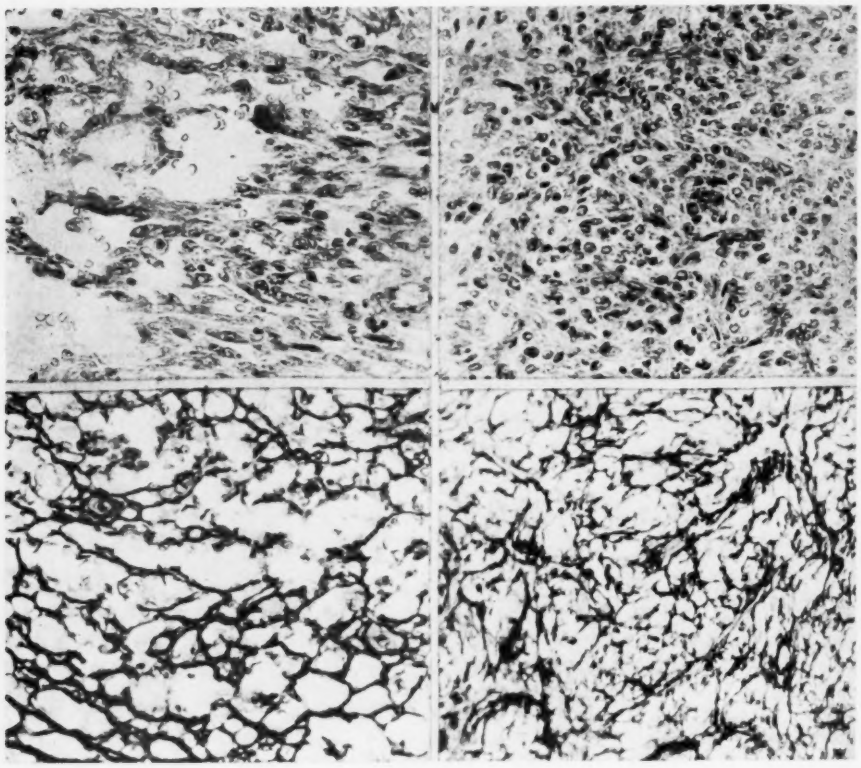
One variety of this tumor manifests a certain degree of constancy in its form. It seems to grow especially in infants, and there are two examples of it represented in the present series (Cases 17 and 18), both of which closely resemble one another in every way. These tumors differ from all of the others in that they both maintain a uniform histologic appearance throughout (Fig. 5 A), so that the illustration furnishes an accurate picture. They are composed of closely packed capillaries, with heaped up endothelia, and a tendency to anastomose, so that they are by definition hemangio-endotheliomas, but growth, although rapid, is orderly, and neither has recurred nor metastasized in the short space of time they have been followed. Nevertheless, one must not assume that this special form always pursues such a benign course. The kindness of Dr. Beryl Paige, Pathologist of the Babies Hospital, has enabled the writer to review the slides of the case of a female baby dying in its fifth month, which was reported by the late Dr. Martha Wollstein (1931) as a "malignant hemangioma of the lung with multiple visceral foci." In this case there were many tumors in skin and viscera, the majority of which were exactly similar to the two tumors here reported, while the rest were simple capillary or cavernous hemangiomas. It is really impossible to decide whether these tumors are multiple independent growths, as seems probable, or whether some of them are metastases. The question of metastasis of a simple hemangioma does not here arise, for the growths are definitely hemangio-endotheliomas.

At this point, it seems pertinent to debate the question of the so-called benign metastasizing hemangiomas. The writer reread the published reports of some of these cases in an effort to determine whether or not he could agree with the authors that the tumors were simple hemangiomas and that they metastasized. The cases of Langhans (1879), Borrmann (1907), Shennan (1914), Wright (1928), and Siirala and Näätänen (1940), all show atypical endothelia and very free vascular anastomoses, which bring them definitely into the class of hemangio-endothelioma. The cases of Weiss (1911), Konjetzny (1912) and Ewing (1928), are not illustrated with photomicrographs, so that the reader cannot judge for himself. Stamm's (1891) thesis was not available.

Robinson and Castleman (1936) reported that the primary tumor in their case was a simple hemangioma, while the metastases were angiosarcomatous. Their illustrations support this contention. It seemed important to review this case to determine whether or not the whole primary tumor appeared like the illustration. Dr. Castleman was kind enough to permit me to examine the original microscopic preparations. They show that in the primary growth there are some areas with extremely free-sprouting and anastomosis of capillaries which are lined with prominent darkly stained endothelia varying in relative size. Thus this case also shows features which lead me to classify it as hemangio-endothelioma and not simple benign hemangioma.

In the present group of tumors, Case 1, which has been reported previously,

with illustrations, by Hill and Stout (1942, Case 25), showed in the primary tumor the formation of a meshwork of anastomosing capillaries lined with deeply stained swollen endothelia, which resemble Robinson and Castleman's tumor and that of Borrmann, and are like Case 3 shown here in Figure 3 C. Such formations do not occur in simple nonmalignant hemangiomas. The picture may be reproduced occasionally in the very rapid formation of capil-



A B

FIG. 4.—Case 8: A (left). Hemangio-endothelioma of erector spinae muscle. Above, the vascular pattern is partly obscured by the sheet-like proliferation of elongated endothelia, but the Laidlaw silver reticulin stain, below, demonstrates its presence.

Case 9: B (right). Hemangio-endothelioma of calf muscles. The endothelia of this tumor form solid cords of cells coursing in various directions. Laidlaw's silver reticulin stain, below, brings out the vascular pattern (see Figs. 6 and 7). (× 525 reduced)

laries which can take place in the organization of intravascular thrombi. But here the growth is strictly limited to the thrombus and never invades surrounding tissues. This comparison emphasizes the fact that in malignant vascular tumors growth takes place by sprouting in the fashion characteristic of the formation of vessels in granulation tissue and not in the way blood vessels are developed in the primitive mesenchyme of the embryo.

Thus, the writer has not been able to find any case which, to him, offers incontrovertible proof of the existence of such an anomaly as a benign metastasizing hemangioma and he, therefore, doubts its existence.

One tumor (Case 9) in this series differs from all the others because the whole tumor is overgrown with elongated cells generally arranged in slender cords which are usually solid but sometimes have a core of red blood cells. In addition, capillaries lined with normal endothelia are frequent in some areas. Laidlaw's silver reticulin stain shows a vague tubular arrangement of reticulin corresponding with the solid cords of cells (Fig. 4 B). Grossly, this tumor was extremely vascular and hemorrhagic (Fig. 7). The morphologic features of this tumor alone would hardly warrant its inclusion in the group of hemangio-endotheliomas. It seems proper to do so, however, because explantation *in vitro* demonstrated that the tumor cells had the characteristics of endothelia. Details are reported in a separate communication (Murray and Stout, 1943).

In all of the tumors here described, and in acceptable previously reported cases, the tumor cells appear as variously illustrated in this paper. There are a few tumors of bone called angio-endotheliomas which have cells of a different aspect. These demand separate discussion.

On page 362 of the 4th Edition of Ewing's "Neoplastic Diseases" there appears an illustration (Fig. 133) labelled "Structure of angio-endothelioma of bone." It shows large clear cells with small nuclei in alveolar arrangement, with red blood cells in the lumens. In the text reference is made to a number of the older surgeons and pathologists who described similar bulky lesions in bones, which they considered primary vascular endotheliomas. Ewing says that he has seen three such cases, but in a final paragraph he warns that such tumors may be confused with metatases from primary growths elsewhere. Thomas (1942), in his paper dealing with vascular tumors of bone, has apparently been influenced by Ewing, for he includes cases which he calls angio-endothelioma. One of them is illustrated and is Bone Sarcoma Registry Case 2156. It formed a bulky tumor in the humerus. Death followed six months after amputation, apparently from heart disease, and there was no autopsy. The photomicrograph shows a tumor exactly like that illustrated by Ewing.

If these tumors are truly hemangio-endotheliomas they differ histologically from any others in other parts of the body, and must be a variety peculiar to bone. They can be explained more easily as metastases. The histologic structure described and illustrated is exactly like hypernephroid carcinoma. Red blood cells in the lumens of the tubules lined by the characteristic clear cells is not an uncommon finding in the primary kidney tumors. Moreover, a solitary metastasis to bone from an occult hypernephroid carcinoma is a well recognized phenomenon. For these reasons it seems improper to accept such cases as hemangio-endotheliomas or, indeed, as vascular tumors at all.

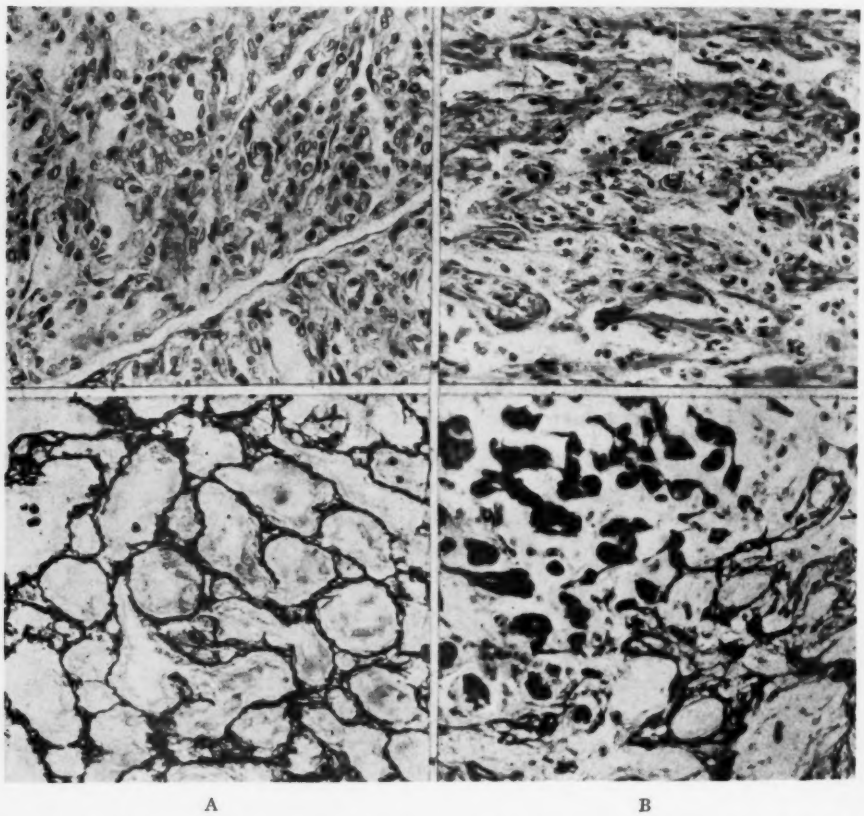
CASE REPORTS

BREAST

Case 1.—J. M., white female, age 19.

Slightly bluish lumps in the right breast, of three months' duration, were treated

for six months with estradiol benzoate without avail. When biopsy showed what was wrongly interpreted as a capillary hemangioma this was stopped and four months later quinine and urethane were injected into the constantly enlarging breast. Five months after biopsy the enormously enlarged, turgid, discolored breast was removed by Dr. D. C. Bull (Fig. 1). It weighed 1647 Gm. and contained a liter of blood. Two months later metastases began to appear, first in the abdominal wall and later in the humerus, scapula and lungs. Before mastectomy the platelets were low and now



A B

FIG. 5.—Case 17: A (left). Hemangio-endothelioma of scalp. Above are shown the vessels with rounded cells surrounding their lumens. One can only be certain that all the encompassing cells are endothelia by using silver to outline the vascular framework, as shown below.
Case 16: B (right). Hemangio-endothelioma of eyelid. Above, is shown the anastomosing vascular channels lined by elongated hyperchromatic endothelia. Some of these are encased by thick collagenous sheaths as shown by the silver stain below (see Fig. 10). (× 525 reduced)

they dropped to 51,000, and ecchymoses appeared on the legs. Three months after mastectomy she died, with symptoms of abdominal hemorrhage.

The breast was honeycombed with blood-filled cavities of all sizes, and these showed a proliferation of rounded and flattened malignant endothelia sometimes heaped up and sometimes in a single layer, quite comparable to the tumor shown in Figure 2 A. The primary growth showed freely anastomosing capillaries lined by swollen elongated endothelia, comparable to Figure 3 C (Hill and Stout: Sarcoma of the Breast, Case 25, illustrated).

Case 2.—J. M., white female, age 65.

A five-centimeter nodule lateral to the nipple in the right breast, with a reddish-

purple hue to the elevated overlying skin and a suggestion of pigskin effect. Radical mastectomy was performed two weeks after onset, and the firm, grayish-white mass was speckled with areas of hemorrhage and yellow foci. There were no axillary metastases found. Microscopically, the growth resembled Case 1. One month later there were recurrences in the scar and lung metastases. Irradiation was without effect, and two months after onset the patient was dead. (Case of Drs. W. C. Seelye and J. P. Beck, Worcester, Mass. Reported by Hill and Stout: Sarcoma of the Breast, with illustration).

Case 3.—A. P., white female, age 68.

Pain in the right breast of two years' duration and a lump which, after a blow some months before, became black and blue and began rapidly to increase in size. It was said to be the size of an orange when simple mastectomy was performed. One month after mastectomy there was a recurrence in the scar, from which blood was aspirated. Three months after mastectomy there were metastases in both lungs and the right ischium. Numerous skin metastases next appeared over opposite breast and forehead. In spite of irradiation therapy with roentgen-ray and radium she died four months after operation. The breast tumor, examined by Dr. A. O. Severance, was 7 x 4.5 x 3.5 cm., and grossly suggested a hemorrhagic fat necrosis. He correctly diagnosed it as malignant hemangio-endothelioma. It closely resembled the two preceding cases (Fig. 3 C). (Case of Drs. C. S. Venable, D. Jackson, and A. O. Severance, San Antonio, Texas).

LIVER

Case 4.—Autopsy 11340: M. B., colored male, age 54.

This syphilitic patient had been under treatment for diabetes for a year. Seven weeks before death he suffered from abdominal cramps, profuse diarrhea and bloody ascites. He failed rapidly, and died without remission of symptoms. At necropsy, the liver weighed 2740 Gm., and measured 29 x 13 x 23 cm. It was filled with large hemorrhagic nodules and smaller hard yellowish-white ones. Metastases were found in pancreas, kidneys, right suprarenal, spleen, diaphragm, lungs, peritoneum, omentum, abdominal skin and abdominal lymph nodes. Microscopically, the tumor is composed of multiple anastomosing vascular tubes lined by large bizarre endothelia which are heaped up in many places. The multiplication of these cells is so great it obscures the tube formation in some areas but its presence is revealed by the silver reticulin stain. The abdominal skin nodules were found around the punctures of the paracentesis needle and may represent tumor implants. (From the Pathology Laboratory of the Presbyterian Hospital. Dr. J. W. Jobling, Director).

Case 5.—Path. 12177: A. C., male, age 52.

Symptoms began with a dragging pain in the right flank one year before death. It gradually became worse, with radiation to epigastrium, loss of weight, darkening of skin, weakness, dizziness and dyspnea. Except for a large liver, no definite findings were recorded. Following cystoscopy, he developed acute uremia and died in a few days. At necropsy, the liver weighed 3020 Gm., and measured 31 x 19 x 10 cm. It contained multiple large and small nodules of yellowish-red hue, found chiefly in the right lobe. The largest was three centimeters in diameter. Metastases were found in the heart and lungs. The tumor is made up of vascular tubes outlined by reticulin fibers, lined with large, swollen, elongated endothelia of bizarre appearance and variable size and shape, which are not heaped up (similar to Fig. 3 A). (From the Pathology Laboratory of the Presbyterian Hospital. Dr. J. W. Jobling, Director).

BONES

Case 6.—L. D., female, age 60±.

Four months before operation pain began in the region of the left external malleolus

and was soon followed by swelling in the lower leg and ankle but not in the foot. No history of trauma. Roentgenograms showed evidence of a destructive central lesion in the lower ends of the tibia and fibula, with widening of the bones. When the marrow cavities of the lower ends of the tibia and fibula were exposed they were filled with a very vascular tissue which looked like sponge rubber. This was curetted out. The wound was packed open because of oozing, with subsequent secondary closure and

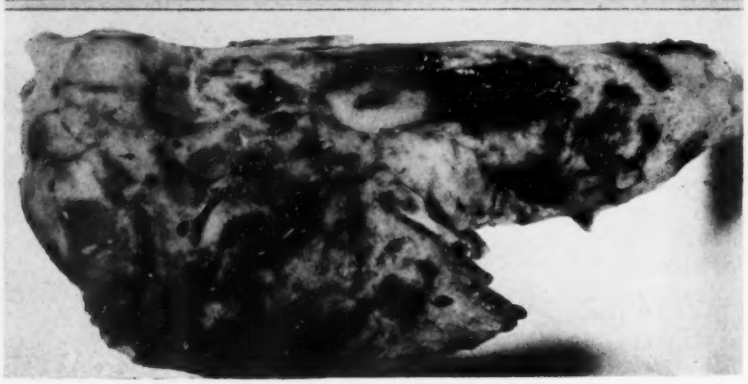


FIG. 6.—Case 9: Hemangio-endothelioma of flexor longus digitorum and flexor longus hallucis muscles in the left calf of a 28-year-old colored male. It was 11.5 cm. larger than the right calf (see Figs. 4B and 7).

Fig. 7.—Case 9: Section of the large tumor showing many hemorrhages, vascular spaces and areas of degeneration (see Figs. 4B and 6).

good healing. Three months after the operation roentgenograms showed what appeared to be an extension of the process in the tibia and fibula and similar areas of rarefaction in all the tarsal and metatarsal bones and a possible area of involvement in the great trochanter of the femur of the same side. She was known to have been alive ten months after operation, but the final result is unknown. The tumor is composed of great numbers of small capillaries which anastomose freely and are lined by prominent hyperchromatic endothelia. These are all elongated and frequently fill and obliterate the lumen. The stroma is often filled with red blood cells. The bony trabeculae show pressure atrophy (Fig. 3 B). (Case of Drs. H. W. Cave, surgeon, and W. Brandes, pathologist of the Roosevelt Hospital, N. Y.).

Case 7.—Young female (20±).

The history of this tumor is not available. It is known to be primary in a rib. It metastasized widely, and killed her in two or three years. The case was studied by Dr. H. E. MacMahon, in the Laboratory of Pathology, Tufts College Medical School, who permits its inclusion in this group. Dr. Frederic Parker called the case to my attention. Histologically, the tumor shows great variability, in some areas the vascular tubes are lined with elongated cells, elsewhere the cells are rounded and heaped-up, and, finally, overproduction of tumor cells in solid masses obscures the vascular tubes.

MUSCLES

Case 8.—J. P., male, age 14.

Eight months before operation this boy fell, striking his side and back. There was not much pain at the time but one week later dull aching in the interscapular region began. It persisted and, finally, a deep mass was felt. Roentgenograms were negative. It was first explored by Dr. W. Darrach, and found to lie in the right erector spinae group of muscles, with its upper end at the level of the spine of T 6. It was dark purple, rubbery, not encapsulated, and about five centimeters in diameter. A biopsy showed that the tumor was malignant, and five days later the mass was excised with the surrounding muscles, but some of it was left behind in the sixth right intercostal muscle. In four months there were evidences of lung metastases and symptoms of paraplegia. Death occurred seven months after operation. This tumor is composed of many vascular spaces outlined by reticulin fibers and lined with both rounded and elongated bizarre endothelia. The vessels are often obscured by an overgrowth of these elongated cells which appear in solid sheets (Fig. 4 A).

Case 9.—M. W., colored male, age 28.

The growth first appeared unexpectedly as a marble-sized lump in the left calf, three years before operation. It was stationary until nine months before when the calf began to swell. Four months before, aspiration yielded only blood. Examination showed a diffuse enlargement of the left calf, which measured 47.5 cm. in circumference, while the right was only 36 cm. (Fig. 6). When a frozen-section showed a malignant tumor, amputation through the middle third of the thigh was performed by Dr. C. D. Haagensen. Eight months later there was no evidence of return. The tumor measured 16 x 13.5 x 6 cm., was exceedingly vascular, with large spaces filled with black, viscid bloody fluid, and lay with the flexor digitorum longus and flexor hallucis longus muscles, from which it had apparently arisen and invaded the overlying soleus and peroneus brevis muscles (Fig. 7). The microscopic picture in this tumor is obscured because of the great degree of overgrowth of elongated endothelia which form apparently solid sheets and cords, with spaces containing red blood cells scattered among them. The Laidlaw silver reticulin stain outlines the vascular tubes (Fig. 4 B), and the diagnosis was made certain by the growth of endothelia from tumor explants *in vitro*, by Dr. Margaret Murray. Details will be given in a separate communication.

UTERUS

Case 10.—A. M. S., married female, age 28.

Thirty-one months before operation she began to have gradually increasing menorrhagia. Seven months before she bled daily for one month. A curettage showed that most of the endometrium was replaced by capillaries, and it was supposed that she had a hemangioma. Bleeding continued, and a month later a second curettage showed persistence of the vascular tumor. During all this time she suffered from attacks of cramping abdominal pain. Just before operation the temperature was 100° F., pulse 140, vaginal bleeding profuse, and there was pain in the chest and cough. At operation, the uterus was soft and enlarged to the size of a three months' pregnancy.

Hemorrhagic implants were found on the lower sigmoid and in the cul-de-sac of Douglas. A supravaginal hysterectomy, right salpingo-oophorectomy, appendicectomy, and biopsy of sigmoid was performed. When the uterus was opened, a reddish, friable tumor mass was found in the endometrium of the fundus. It penetrated the myometrium. Several other similar, but smaller foci were found in the left cornu and on the posterior wall. Nine months later, metastases were found in the left scapula and still later in both lungs, peritoneum and pelvic bones. She became too anemic to tolerate roentgenotherapy. She died 14 months after operation. This tumor throughout its course shows the same histologic picture. It is composed of capillaries lined by

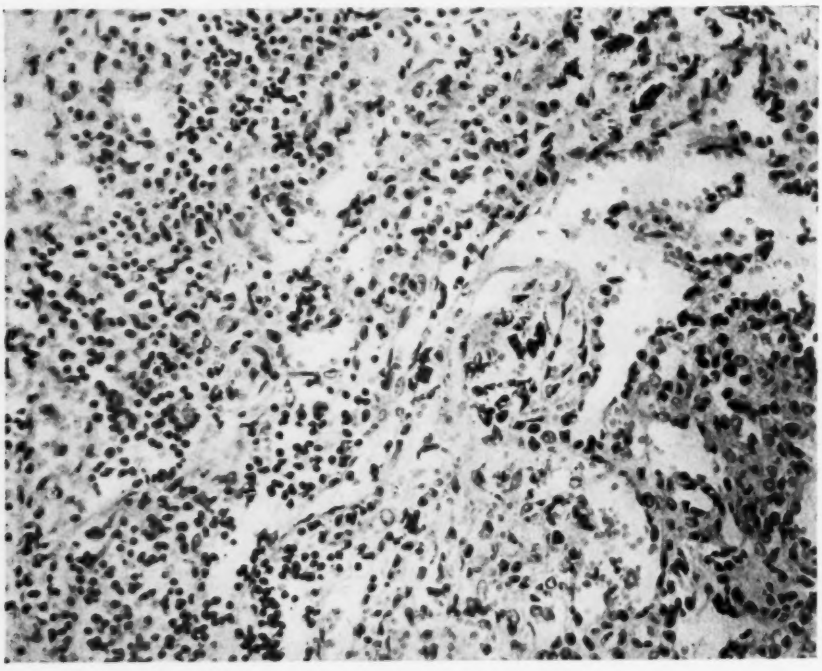


FIG. 8.—Case 11: Hemangio-endothelioma of pleura. Metastasis in a hilar lymph node. Capsule and marginal sinus at left; anastomosing tumor vessels lined with bizarre endothelia at right.

swollen, elongated, hyperchromatic bizarre endothelia showing great variation in size and frequent mitoses. The cells are almost always in a single layer and there is little tendency to heap-up or invade outside the vessel wall. The tumor shows marked infiltrative tendencies (Fig. 3 A). (This case was treated in Sloane Hospital, N. Y., by Dr. B. P. Watson, Director, and is included with his permission).

PLEURA

Case 11.—T. T., male, aged 61.

Eight months before death, pains began in left lower chest, followed by night sweats, weakness and hemoptysis. Two months before death, he entered the hospital, and bloody fluid was repeatedly removed from the left pleural cavity. It was felt that he had a cancer of the lung. After a progressive downhill course he died at the Lincoln Hospital, and was autopsied by Major Chester R. Brown, N. Y., who permits me to include this case. The entire left pleura, both visceral and parietal, was markedly thickened by the hemorrhagic tumor. Metastases were found in the hilar lymph nodes (Fig. 9) and the left lung, and the diaphragm was invaded. In

addition, simple cavernous hemangiomas were found in the diaphragm. This tumor consists, basically, of freely anastomosing vascular tubes lined by atypical endothelia which sometimes are rounded and heaped-up and sometimes flattened, forming a one layer membrane (Fig. 8).

ORBIT

Case 12.—I. P., female, age 40.

She suffered for two years from swelling of the left upper eyelid, with proptosis and double vision during the last three months. Roentgenograms showed an enlargement of the left orbit. At operation, by Dr. G. M. Bruce, a firm mass extended along the roof on the nasal side, from the apex nearly to the anterior orbital margin. Although adherent, it was excised, and measured two centimeters in length. Following this she got a complete paralytic ptosis. Eighteen months later an attempt to correct this by operation failed because of tumor recurrence. A second attempt to excise this was made three years after the first operation. This failed because the growth now infiltrated the medial rectus muscle and the optic nerve. When last seen, six years after the first operation, the globe was fixed and immobile and the ptosis persisted. The tumor appears the same in both manifestations. It consists of freely anastomosing vascular channels occasionally lined by swollen rounded heaped-up endothelia but often obscured by an overgrowth of elongated endothelia. (Case treated at the Institute of Ophthalmology, N. Y., and included by permission of Dr. J. H. Dunnington, Clinical Director).

SUBCUTANEOUS TISSUE AND SKIN

Case 13.—W. R., male, age 25.

For two years there had been a swelling in the right supraclavicular fossa, which slowly increased in size, without symptoms, until three months before operation, when pain radiated from it down to the wrist. This disappeared in three weeks but tenderness remained. When examined it was five centimeters in diameter. At operation, the mass appeared like a dark red plum, and was very vascular. It was excised with an adjacent lymph node. When the nature of the growth was determined and direct invasion of the lymph node recorded, the lymph nodes of the right lower neck were removed. No metastases were found. Thirty-seven months after operation metastases appeared in both ischia, left pubis, L 2, L 4, sternum and 6th rib. These were treated by irradiation, with some improvement, so that the man could continue his work. Four years after operation there were lung metastases. He finally died, five years and two months after operation. There was no autopsy but biopsy of a rib confirmed the fact of metastasis. The tumor is made up of freely anastomosing vascular tubes sometimes lined by a single layer of prominent hyperchromatic, flattened endothelia but usually by rounded, swollen, heaped-up tumor cells of varying size (Fig. 2 A). (Three months after the first operation the case was reported Dr. J. M. Hanford).

Case 14.—H. G., colored female, age 49.

She received a blow on the medial aspect of the left knee region two years before admission. This was immediately followed by ecchymosis. Two months later attacks of throbbing pain began and lasted for 16 months, when swelling began, and all symptoms grew worse. Examination showed a diffuse swelling of the posteromesial aspect of the left popliteal region. There were extensive varicosities in this extremity. The lesion was explored, and a large multilocular cystic cavity found containing from 300 to 400 cc. of old blood. It was supposed to be a hematoma. The blood was evacuated and the wound closed. Later, it broke open again and drained foul-smelling bloody material, while the pain and swelling increased. Ten months later, at a second operation, by Dr. A. H. Blakemore, a tumor eight centimeters in diameter was found. It was subcutaneous, sharply circumscribed, and involved the deep fascia. It was excised.

Sixty-seven months after excision there was no evidence of recurrence. The tumor consisted of a spongy mass of intercommunicating cavities filled with blood. A thick-walled vein entered the upper pole of the mass (Fig. 9). Microscopically, this tumor shows numerous vascular tubes which often anastomose and are lined by heaped-up rounded endothelia. In many areas the endothelia have multiplied to such an extent that the lumens are solidly filled, and only the silver reticulin stain demonstrates them by accentuating the fibrous framework (Fig. 2 B).

Case 15.—Female, age 35.

Seven months before operation several nodules developed in the scalp above the right ear. These were diagnosed as "cysts," and biopsy is said to have been taken but no report is available. Soon after, swellings appeared in the right neck. All were firm, circumscribed and somewhat painful and tender. A neck mass, midway between angle of jaw and clavicle, was explored. It was apparently encapsulated, 3 x 2 x 0.5

FIG. 9.—Case 14: Hemangio-endothelioma of popliteal region. Cross-section of the tumor tissue, its multiple cavities and the large vein, which entered its upper pole shown at the right (see Fig. 2B).

cm., and lay deep to, but not attached to, a branch of the cervical plexus. It was described as hemorrhagic. The patient was not followed. The tumor is composed of the usual widely anastomosing vascular spaces lined by rounded and polygonal cells, often heaped-up and sometimes forming papillary processes. (Case from the Hospital of the University of Pennsylvania. Reported by permission of Drs. Louis Kaplan, surgeon, and R. H. Horn, surgical pathologist).

Case 16.—S. K., female, age 17.

Ever since birth there had been a "hemangioma" of the lateral aspect of the right upper eyelid. Prior to her first operation, at the Presbyterian Hospital, there had been six previous attempts at surgical removal, all of which failed. At this time, the tumor measured 15 x 10 x 5 mm. It was excised but promptly recurred (Fig. 10). The 8th and 9th attempts were made, respectively, one year and 16 months after the 7th attempt. She was not followed after this last operation, when she was 20 years old. Grossly, the tumor was composed of firm hemorrhagic tissue. This tumor is made up in part of large, cavernous vascular spaces filled with blood and in part of a spongy meshwork of very freely anastomosing capillaries lined by swollen elongated endothelia frequently heaped-up in layers. The capillary sheaths are sometimes greatly thickened and seemingly hyalinized (Fig. 5 B). (From the Ophthalmological Service of the Presbyterian Hospital. The late Dr. John M. Wheeler, surgeon).

Case 17.—W. W., female, age 3 months.

A red spot was present at birth in the skin of the right parietal region. It was one centimeter in diameter and increasing rapidly in size when it was excised. It lay in the skin and did not seem to have any deep connections. No recurrence after 30 months. The growth infiltrates the structures of the skin quite freely without destroying them. It consists of numerous closely placed blood vessels lined with heaped-up rounded endothelia, the most internal layer of which tend to be elongated. This makes it appear in ordinary stains as if the vessel is surrounded by pericytes. Because of this the tumor at first was called a hemangiopericytoma (Stout and Murray, 1942, Case 3). The silver reticulin stain shows that all of the cells are inside of the reticulin sheaths and are, therefore, endothelia (Fig. 5 A). (From the Nix Hospital, San Antonio, Texas. Drs. L. J. Ross, surgeon, and A. O. Severance, pathologist).

Case 18.—D. R., male, age 11 months.

When the child was three months old, the mother noted a swelling over the inner angle of the left eyebrow. Slow increase to 25 mm. diameter. It was subcutaneous, with normal overlying skin, and was mistaken for a dermoid cyst. No recurrence one year after excision. Microscopically, the growth exactly resembles Case 17, except that it is subcutaneous instead of intradermal. Only a few of the vessels have visible lumens containing red blood cells, because multiplication of the endothelia has solidly filled them. The silver reticulin stain shows the true state of affairs. (Case from Babies Hospital, Dr. B. Paige, pathologist).

SUMMARY

Hemangio-endothelioma is the most common type of the malignant vascular tumors but, even so, it is a relatively rare neoplasm. It has a wide distribution in the various organs and tissues of the body, and may manifest itself at any age, although half of the cases occur in childhood or youth. Growth may be rapid or slow, and is infiltrative in character. When approached, the tumors are usually, but not always, obviously vascular, with a tendency to bleed into themselves or from the surface. Metastasis is common and is generally through the blood stream although occasionally it progresses also through the lymphatics.

The tumors are made up of congeries of vascular tubes which have a marked tendency to anastomose and are lined with hyperchromatic atypical endothelial tumor cells. These may be of any shape and size. They may form a single layer, be heaped-up in several layers, or even multiply to such a degree that the vascular tubes are completely obscured, when ordinary stains are used, and can only surely be demonstrated by silver connective tissue impregnations. The same tumor may show two or more of these variations in the primary growth and the metastases. No tumor should be called a hemangio-endothelioma unless it fulfills these microscopic criteria and, conversely, if a tumor does show these characteristics it should be recognized as a malignant or potentially malignant tumor. There is no such anomalous entity as a benign metastasizing hemangioma. Two other tumor forms especially have been confused with this one, namely, chorio-epithelioma and hypernephroid carcinoma. If the criteria already given are strictly applied, one should be able to avoid this error. The hemangio-endothelioma of

infants apparently is better differentiated and probably less malignant, although it may kill by the multiplicity of its tumors, as occurred in Wollstein's case. The silver reticulin stain is of particular assistance in aiding one to distinguish hemangio-endothelioma from hemangiopericytoma, since endothelia are found inside and pericytes altogether outside the reticulin sheath of the vessels. Demonstration that tumor cells behave *in vitro* like endothelia provides further confirmatory evidence.

FIG. 10.—Case 16: Hemangio-endothelioma of the right eyelid in an 18-year-old girl. It was present at birth, and seven previous operations had failed to eradicate it (see Fig. 5B).

BIBLIOGRAPHY

Bary, E. de: Über zwei Fälle von malignem Hämangioendotheliom. Frankfurt Ztschr. f. Path., **46**, 410, 1934.

Beitzke, H.: Ein metastasierendes Angiosarkom. Virchows Arch. f. path. Anat., **287**, 82, 1932.

Borrmann, R.: Metastasenbildung bei histologisch gutartigen Geschwülsten (Fall von metastasierendem Angiom). Beitr. z. path. Anat., **40**, 372–392, 1907.

Cannata, G. M.: Emangioendotelioma retroduodenale e sintomatologia di Colelitiasi. Pathologica, **23**, 585, 1931.

Ewing, J.: Neoplastic Diseases. W. B. Saunders Co., Phila., and London, 4th Ed. 1940; page 255, 362.

Foulds, G. S., and Flett, R. H.: Endothelioma of the Corpora Cavernosa. J. Urol., **40**, 826, 1938.

Fourmestraux, J. de, and Foulon, P.: Étude des différentiations cellulaires multiples dans une tumeur mésenchymateuse. Bull. Assoc. franç. p. l'étude du cancer, **19**, 386, 1930.

Gloggengiesser, W.: Angiomartige Umwandlung des Gefässmesenchyms als Systemerkrankung. Beitr. z. path. Anat. u. z. allg. Path., **103**, 256–270, 1939.

Grandclaude, Ch., Lambert, M., and Driessens, J.: Les sarcomes du pancréas (à propos d'un cas d'angio-myo-sarcome due pancréas). Ann. d'anat. path., **10**, 860, 1933.

Gross, P., and Englehart, C. E.: Primary Hemangio-endothelioma of Heart. Am. J. Cancer, **30**, 102, 1937.

Hall, E. M.: Malignant Hemangioma of the Lung with Multiple Metastases. Am. J. Path., **11**, 343, 1935.

Hanford, J. M., Malignant Hemangio-endothelioma of Neck. ANNALS OF SURGERY, **110**, 136–138, 1939.

Hewer, T. F., and Kemp, R. P.: Malignant Hemangio-endothelioma of the Heart: Report of a Case. J. Path. & Bact., **43**, 511, 1936.

Hill, R. P., and Stout, A. P.: Sarcoma of the Breast. Arch. Surg., **44**, 1, 1942.

König, E.: Sarkome der Vena cava inf. Chirurg., **3**, 104, 1931.

Konjetzny, G. E.: Zur pathologie der Angiome. München. med. Wchnschr., **59**, 241, 1912.

Langhans, T.: Pulsirende cavernöse Geschwulst der Milz mit metastatischen Knoten in der Leber. Virchows Arch., **75**, 273, 1879.

Leubner, H.: Seltene Geschwulstbildungen des Gefässendothels. Frankfurt. Ztschr. f. Path., **49**, 63, 1935.

Leuret; Leroux, R; Theillier et Busser: Angiomyosarcome de la cuisse. Bull. Assoc. franç. p. l'étude du cancer, **19**, 272, 1930.

Magnusson, R.: Sarcoma of Small Intestine: In Connection with Case of Haemangiosarcoma of Jejunum. Acta Chirurg. Scand., **73**, 576, 1934.

Mallory, F. B.: The Results of the Application of Special Histological Methods to the Study of Tumors. J. Exper. Med., **10**, 575, 1908.

Molotkoff, W. G.: Zur Gewebsherkunft chorionepitheltiom-ähnlicher Geschwülste. Virchows Arch. f. path. Anat., **288**, 317, 1933.

Murray, M. R., and Stout, A. P.: The Glomus Tumor: Investigation of its Distribution and Behavior, and the Identity of its "Epithelioid" Cell. Am. J. Path., **18**, 183, 1942.

Murray, M. R., and Stout, A. P.: Cultural Characteristics of a Hemangio-endothelia. Am. J. Path., 1943 (in press).

Ogilvie, R. F., and MacKenzie, I.: Malignant Hemangio-endothelioma: With Report of Two Cases. J. Path. & Bact., **43**, 429, 1936.

Plaut, A.: Hemangio-endothelioma of Lung: Two Cases. Arch. Path., **29**, 517–529, 1940.

Rabson, S. M.: Multiple Mesenchymal hemendothelioma. Arch. Path., **25**, 185, 1938.

Ransom, H. K., and Samson, P. C.: Malignant Tumors of the Greater Omentum. ANNALS OF SURGERY, **100**, 523, 1934.

Robinson, J. M., and Castleman, B.: Benign Metastasizing Hemangioma. ANNALS OF SURGERY, **104**, 436, 1936.

Sal, J.: Uber einen Fall von endemischer Hämangiosarkomatose bei Hühnern. Virchows Arch., **279**, 62, 1931.

Scheidegger, S.: Malignes Hämangioblastom des Perikards. (Beitrag zur Frage der Deckzellengeschwülste). Frankfurt. Ztschr. f. Path., **51**, 286, 1937.

Shaw, J. J. M.: Haemangioma. Lancet, **1**, 69, 1928.

Shennan T.: Histologically Nonmalignant Angioma, with Numerous Metastases. J. Path. & Bact., **19**, 139–154, 1914.

Sherrill, G., and Graves, F. S.: Haemangio-endothelioblastoma of the Stomach. Surg., Gynec. & Obst., **20**, 443, 1915.

Sovak, F. W., and Carabba, V.: Hemangio-endothelioma Intravasculare of Ovary: Review of Literature, with Report of Case. Am. J. Obst. & Gynec., **21**, 544, 1931.

Stamm, C.: Beiträge zur Lehre die Gefässgeschwülsten. Inaug. Diss., Göttingen, 1891.

Stout, A. P.: Solitary Cutaneous and Subcutaneous Leiomyoma. Am. J. Cancer, **29**, 435, 1937.

Stout, A. P.: Leiomyoma of the Oral Cavity. Am. J. Cancer, **34**, 31, 1938.

Stout, A. P., and Murray, M. R.: Hemangiopericytoma. ANNALS OF SURGERY, **116**, 26, 1942.

Thomas, A.: Vascular Tumors of Bone: Pathologic and Clinical Study of 27 Cases. Surg., Gynec. & Obst., **74**, 777, 1942.

Turner, O. A., and Kernohan, J. W.: Vascular Malformations and Vascular Tumors Involving the Spinal Cord: Pathologic Study of 46 Cases. Arch. Neurol. & Psychiat., **46**, 444–436, 1941.

Weiss, S.: Metastasierendes Angiokavernom als Todesursache. Med. Klinik, **7/2**, 1273, 1911.

Wollstein, M.: Malignant Hemangioma of the Lung, with Multiple Visceral Foci. Arch. Path., **12**, 562, 1931.

Wright, A. W.: Primary Malignant Hemangioma of the Spleen, with Multiple Liver Metastases. Am. J. Path., **4**, 507, 1928.

VENOUS HEMANGIOMA OF SKELETAL MUSCLE

CASE REPORT

RUDOLPH A. LIGHT, M.D.

NASHVILLE, TENN.

FROM THE DEPARTMENT OF SURGERY, VANDERBILT UNIVERSITY MEDICAL SCHOOL, NASHVILLE, TENN.

VENOUS HEMANGIOMATA of skeletal muscle are not common. Jenkins and Delaney[1] reviewed 256 cases in 1932. Oughterson and Tennant,[2] in 1939, state that nearly 300 cases have appeared. Since that time seven other cases, three by Sorenson,[3] and four by Fulton and Sosman,[4] have been reported. Several other titles of papers not available to the author are listed in The Quarterly Cumulative Index.

The lesion occurs nearly twice as often in the leg as in the arm, and has a predilection for larger muscles.[2] It is now generally conceded that the condition is congenital but the reason for the delay of onset of symptoms is not known. Trauma certainly is a dubious cause, appearing in only 17 per cent of cases.[1] The onset of symptoms in 79 per cent of cases is before the twentieth year, and in 94 per cent is before the thirtieth year.[1]

The most frequent symptom was pain (70 per cent), but in only a few cases was this of paroxysmal character. Stout,[5] in his analysis of 2080 tumors of skin and subcutaneous tissues, found 20 instances (one per cent) in which paroxysmal pain was present—glomus tumors (angiomyoneuromata) nine; leiomyomata, nine; hemangiomata, two; fibroma, keloid, sebaceous cyst, dermoid and neurofibroma, one each.

FIG. 1.—Showing flexion of knee, plantar flexion contracture at ankle, and "tip-toe" deformity.

Deformity and impairment of function occurred in 50 of Jenkins and Delaney's 256 cases (23 per cent). A case similar to the one described herewith was reported by Josefsson[6] in 1928.

Case Report.—V. U. H. No. 107121: C. N., white, male, age 16, was admitted to the hospital May 10, 1940. He had noted two years previously, without previous trauma, a slightly tender area on the posterior lateral surface of the right knee. Tenderness persisted and increased in severity. For the past year he had experienced pain in the region, which, in the beginning, was paroxysmal in character. He had

noted nothing which would cause onset of pain. There was at no time evidence of inflammation or a palpable mass. During the past six months the pain had increased in severity and seemed to be made worse by standing. For the past three months it had been of such severity that he walked on the toe of his foot and used a "cane." In the past two months ambulation had become almost impossible, and he stated that he kept the leg flexed at the knee to alleviate the pain.

Physical examination revealed no abnormalities except of the right lower extremity. The patient lay in the bed with the right knee flexed. He was extremely apprehensive when the leg was approached, resisted all efforts to straighten it out, and cried out with pain frequently. There was a plantar flexion contracture at the ankle, and Figure 1 shows the "tip-toe" deformity. The right calf was three centimeters smaller than the left, but otherwise the extremities were symmetrical.

There was an area of excruciating tenderness over a three-centimeter area just

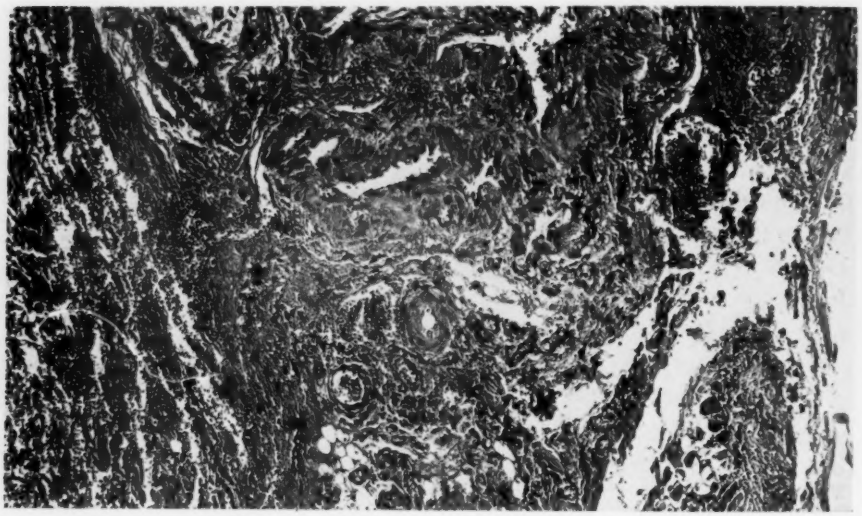


FIG. 2.—Showing infiltration of muscle by thick-walled vessels; capillary and cavernous endothelial-lined spaces, some containing blood, and some fibrosis.

behind and medial to the head of the fibula. This corresponded to the area of his pain. No palpable mass was present. Reflexes were normal and no sensory abnormalities, consistent with peripheral or central nervous system disease, were revealed. Skin temperatures of the two extremities were normal. Laboratory studies were not significant, and roentgenograms showed no abnormalities.

A diagnosis of glomus tumor was made and May 15, 1940, operation was performed by Dr. Barney Brooks. Under local anesthesia, an incision was made through skin, subcutaneous tissue and fascia over the point of maximum tenderness. Pressure on the lateral head of the gastrocnemius caused severe pain. On inspection of the deepest surface of the muscle, there was found an area, approximately 2 x 3 centimeters, having the appearance of cavernous hemangioma in which were flecks of yellowish tissue. No connection with the peroneal or posterior tibial nerves or vessels could be demonstrated. All the abnormal tissue was excised, after the administration of a general anesthetic.

After operation, traction was applied to the leg, and the foot was kept at right angles to the leg for six days. He began walking on the seventh day, with still considerable flexion deformity of the knee and with pain in the region of the wound. He was discharged on the ninth postoperative day, at which time he still experienced

pain exactly as before operation. He was examined two years and ten months after operation, at which time the only abnormality present was the defect in the medial aspect of the lateral head of the gastrocnemius muscle. The patient had not experienced any pain since discharge from the hospital. The flexion deformity of the knee gradually had disappeared during a period of three to four months.

Pathologic Report.—Gross: The specimen consists of a mass of skeletal muscle, 2 x 2 x 0.5 centimeters. At one end, and in the midportion, several bluish areas are present having the appearance of dilated blood vessels. No definite capsule is present.

Microscopically, sections show invasion of muscle by numerous blood vessels, varying in size from capillaries to fairly large arteries and veins. There is considerable smooth muscle between the vessels and in some areas epitheleoid cells are present about the vessels. The striated muscle reveals considerable degeneration. There is a pacinian corpuscle near the area of invasion. *Pathologic Diagnosis:* Glomus tumor.

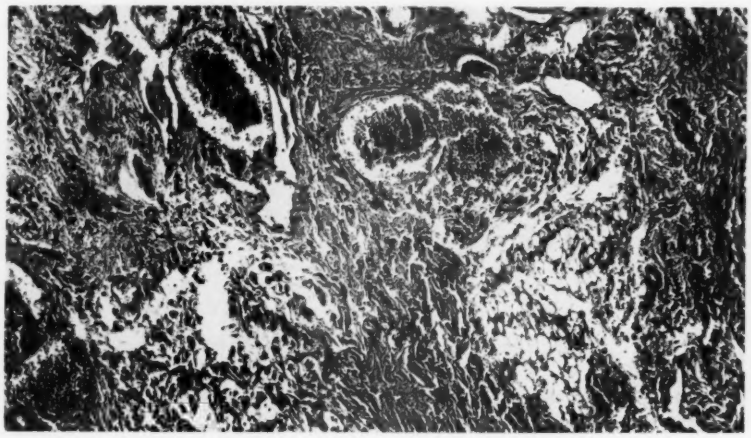


FIG. 3.—Showing cavernous and capillary hemangiomatous infiltration, with an area of fatty infiltration.

DISCUSSION

This case was deemed of interest since only three instances of glomus tumor in deep structures, away from the ends of the extremities, appear in the literature,[7, 8, 9] and only one[9] is this country. However, on review of the published reports of these cases there was considerable doubt in the author's mind as to the correctness of the diagnosis. Murray and Stout,[10] in 1942, have identified the epitheleoid cell of the glomus tumor as the pericyte of Zimmermann. Stout has investigated the *tuberculum dolorosa*[5, 10, 11] extensively, and is certainly an authority on them. The sections from this case were sent to Doctor Stout, who very kindly examined them, and expressed the opinion that this was a case of venous hemangioma[12] because the pericytes (if any) do not regularly surround all vessels. He also rejected the diagnosis of hemangiopericytoma, recently described by Stout and Murray.[13]

As noted above, hemangiomata are a rare cause of paroxysmal pain, such as occurred in this case, being found in only 0.01 per cent of 2081 cases[5] (five per cent of 40 cases in which presence of pain was specified) of cutaneous and subcutaneous tubercles. Stout[5] was unable to attribute the pain experienced in his cases to any one physical abnormality. The fact that our case continued to have pain for a period of two weeks after extirpation

of the tumor, is suggestive that, here, a nervous mechanism was the cause of pain and painful impressions continued to be transmitted during the healing period. This is apparently the fourteenth case of a typical *pes equinus* deformity due to hemangioma of the calf muscles[16] and this lesion, although rare, should be taken into consideration in determining the cause of this deformity. A correct preoperative diagnosis has been made in only 18 per cent of reported cases of angioma of skeletal muscle. The presence of a palpable mass and roentgenologic evidence of phleboliths are the only objective manifestations of this lesion.

Since these lesions produce a great amount of disability, which is almost certainly relieved by excision, correct diagnosis and treatment is very important.

SUMMARY

1. A case of venous hemangioma of the gastrocnemious muscle is presented.

2. The "tip-toe" deformity exhibited by this patient has been reported in thirteen other identical cases.

3. The paroxysmal pain which is characteristic of glomus tumors and some leiomyomata may also occur in hemangiomata, and less frequently in other tumors.

4. Dramatic relief from marked disablement is possible by extirpation of these tumors.

BIBLIOGRAPHY

1 Jenkins, H. P., and Delaney, L. A.: Benign Angiomatous Tumors of Skeletal Muscle. Surg., Gynec. & Obst., **55**, 464, 1930.

2 Oughterson, W., and Tennant, R.: Angiomatous Tumors of Hands and Feet. Surgery, **5**, 73, 1939.

3 Sorenson, Franz: Hemangiome Der Hendmuskeln Klin Wachen, **9**, *222*, March, 1941.

4 Fulton, M. N., and Sosman, M. C.: Venous Angiomas of Striated Muscle. J. A. M. A., **119**, 319, 1942.

5 Stout, Arthur P.: The Painful Subcutaneous Tuburcle. Am. Jour. Cancer, **36**, 25, 1939.

6 Josefsson, Henry: Angioma of the Muscles of the Calf as the Cause of *Pes Equinus*. Acta. Orthop. Scandinav., **8–9**, 219, 1937–38.

7 Thomas, André: Tumeurs compàrables à des tumeurs glomiques dèvelopées dans les muscles de la cuisse à la suite d'un traumatisme. Ann. d'anat. path., **10**, 657, 1938.

8 Bergstrand, A.: Multiple Glomus Tumors. Am. Jour. Cancer, **29**, 470, 1937.

9 Hoffmann, H. O. E., and Ghormley, R.: Glomus Tumor and Intramuscular Lipoma. Proc. Staff Meet. Mayo Clinic, **16**, 13, 1941.

10 Murray, M. R., and Stout, A. P.: The Glomus Tumor: Investigation of its Distribution and Behavior, and the Identity of its "Epithelioid" Cell. Am. Jour. Path., **18**, 183, 1942.

11 Stout, A. P.: Solitary Cutaneous and Subcutaneous Leiomyoma. Am. Jour. Cancer, **29**, 435, 1937.

12 Stout, A. P.: Personal communication.

13 Stout, A. P., and Murray, M. R.: Hemangiopericytoma: A Vascular Tumor Featuring Zimmermanns Pericytes. ANNALS OF SURGERY, **116**, 26, 1942.

14 Davis, J. S.: Primary Hemangiomata of Muscle. Bull. Johns Hopkins Hosp., **19**, 74, 1908.

15 Davis and Kitlowski, E. A.: Primary Intramuscular Hemangiomas of Striated Muscle. Arch. Surg., **20**, 39, 1930.

VENOGRAPHY*

I—ITS USE IN THE DIFFERENTIAL DIAGNOSIS OF THE PERIPHERAL VENOUS CIRCULATION

II—A SIMPLIFIED TECHNIC

JEROME MARK, M.D.†
DETROIT, MICH.

THE ELUCIDATION of many of the problems in the study of the venous return in legs which present varicosities, massive edema, and ulceration has been made by certain excellent clinical tests. The observations of Trendelenberg, Perthes, and Homans have done much to clarify these situations.

In spite of painstaking study, however, it is not possible, in all cases, to determine the status of the venous circulation with certainty by clinical methods alone. In many cases several logical possibilities present themselves. It has been possible in our clinic to demonstrate the exact status of the venous return by venography.

J. C. Dos Santos[1] has described an excellent method for the roentgenologic study of the veins of the lower leg. This method was modified by Bauer,[2] and utilized by others,[3, 4] for the study of postoperative deep venous thrombosis.

The technic is quite simple. The heel is elevated on a six-centimeter block and rests on its mesial surface. Under local anesthesia, a two-centimeter incision is made about one centimeter behind the external malleolus. The lesser saphenous vein is isolated here. It drains into the deep venous system. The distal portion is tied with fine silk, and a small cannula is inserted into the proximal portion. Twenty cubic centimeters of a 35 per cent diadrast solution (Winthrop‡) in injected. The injection rate is uniform and takes about 60 seconds. The roentgenogram is taken during the injection of the last few cubic centimeters. By using a 14 x 17 film in its longest dimensions, and placing the lower end eight to ten centimeters above the ankle it is possible to visualize the deep venous circulation of the calf and a good portion of the femoral vein. The cannula is removed and the vein tied. The skin is closed with silk after lavage of the tissues with saline to remove any residual diodrast, which is quite irritating to the tissues.

We have found it possible, in most cases, to modify this technic by direct venopuncture into a superficial vein on the lateral side of the ankle. With a tourniquet around the ankle, a No. 21–22-gauge needle is inserted into the most prominent vein on the anterolateral surface of the ankle. The tourniquet is then released and the remainder of the procedure is completed as described. This obviates the necessity of incision in most

* Prize Essay, North End Clinic, Detroit, Michigan, July, 1942.

† Lieutenant, M.C., att. 39th Evacuation Hospital, Camp Atterbury, Indiana.

‡ Kindly supplied by the Winthrop Chemical Co. for this problem.

cases. We have also found that better visualization of the deep venous tree is secured by an exaggerated Trendelenberg position. The application of a tourniquet below the groin prevents loss of the dye before the picture is taken and causes more complete filling of the deep system. This has revealed complete filling of the calf veins in a case (Case 3) which appeared to show deep calf thrombosis by the usual technic. We have had no reactions with the diadrast and no evidence of thrombosis following its use.

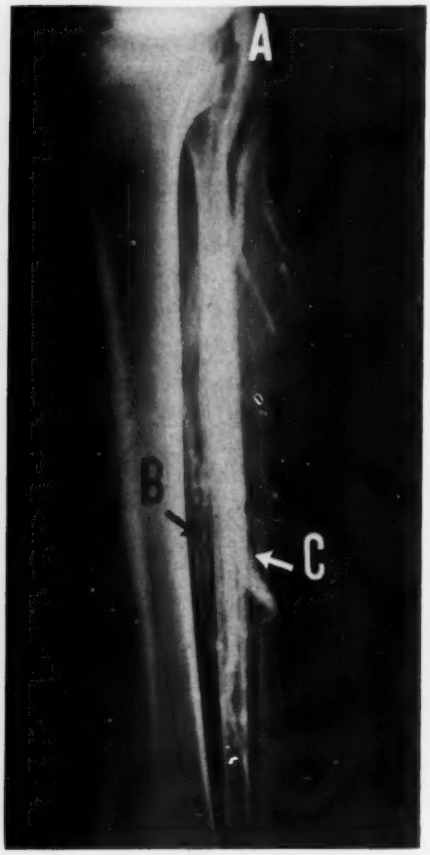


FIG. 1.—A normal deep venous tree in a patient with varicose veins. (A) Popliteal vein. (B) Anterior tibial vein. (C) Posterior tibial vein.

The following cases present a few of the problems which we felt have been clarified by the use of venography.

ILLUSTRATIVE CASE REPORTS

Case 1.—D. K. is a patient with varicose veins but no leg swelling or clinical evidence of impairment of the deep venous circulation. A venogram was taken by employing the usual technic to demonstrate the intact deep venous system. This shows complete filling of the venous tree (Fig. 1).

Case 2.—J. F. is a 50-year-old male, with a chief complaint of painful left leg. The patient had had varicose veins for at least 12 years. These were treated by ligation, with a series of circular incisions in the middle and upper right leg and lower thigh in 1931. The legs contained to swell and became worse after a series of six injections. They became very painful. *Examination* reveals reddish-brown induration in lower half of right leg and ankle. Prominent varicose veins present on medial aspect of lower thigh extending to calf. Questionable positive Trendelenberg test obtained in right leg. During the course of treatment Unna boots were applied. The patient had recurrent attacks of superficial phlebitis. Ace bandages made the extremities more painful.

A venogram was made which showed only a short segment of the deep system communicating with a large dilated superficial varicose vein carrying the entire venous return of the extremity (Fig. 2).

COMMENT: This case presented a problem in diagnosis because of the presence of a large varicose vein which was thought to play a rôle in this patient's symptomatology. It was even suggested that ligation of this vessel should be done before the picture was seen. The roentgenogram,

however, showed, quite convincingly, a condition which necessitated the complete function of these "compensatory superficial varicosities." All occlusive methods of therapy were then abandoned with moderate relief of symptoms.

Case 3.—F. D. This 18-year-old girl noticed left calf hypertrophy for one year. No other complaints. Past history was noncontributory. No history of trauma, phlebitis, or diphtheria. *Examination* reveals marked enlargement of the entire left

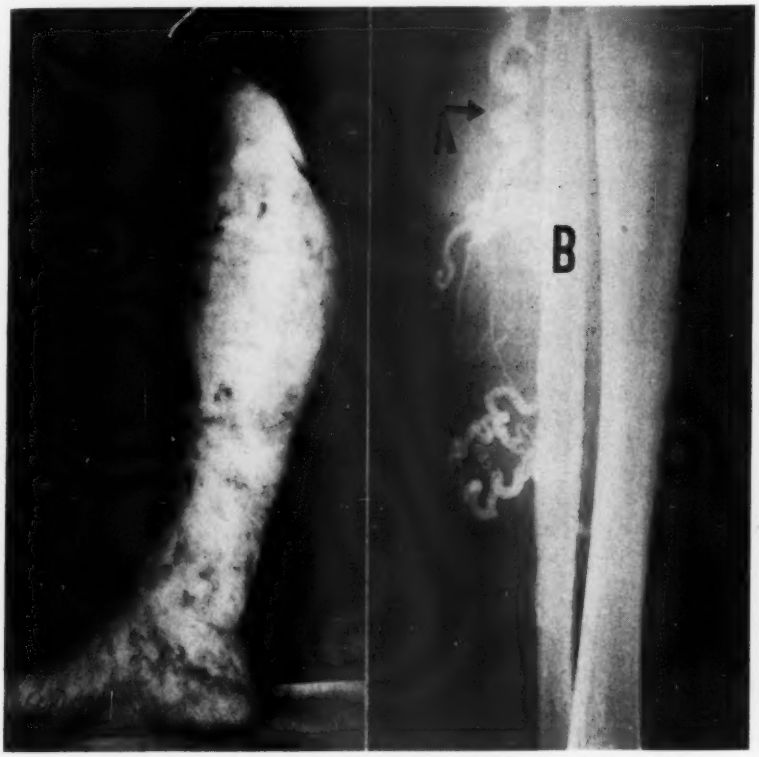


FIG. 2.—Obstruction of the deep venous system with compensatory varicosities. (A) Large superficial varicosity; the only venous return from the leg. (B) Communicator to the small remaining segment of posterior tibial vein.

leg with pronounced calf hypertrophy and varicosities. No tap impulse in the thigh. Questionable fibrous mass in the calf. A roentgenogram of the leg showed thickening of the soft tissues. A venogram showed complete absence of the deep venous system and numerous prominent superficial vessels ending in teat-like projections. A venogram was made of the opposite leg to rule out any bilateral congenital venous abnormality. This was normal. A diagnosis of deep thrombosis with compensatory varicosities was made. A biopsy was advised to rule out angioma.

COMMENT: Several months later another check-up venogram was done on this leg because of the several suspicious teat-like projections of the superficial vessels. At this time a tourniquet was applied below the groin and a picture taken in Trendelenberg position. This roentgenogram revealed complete filling of the deep venous system. There were several marble-

size venous outpocketings in the deep vessels above the knee with numerous intercommunications; a picture which we have not seen before. Exploration was suggested but has not been done (Fig. 3).

Case 4.—A. W., a 48-year-old female, had a "milk leg" 16 years ago. This was followed by varicosities. A high saphenous ligation was performed, with relief of discomfort. There was then a recurrent right internal saphenous vein from the midthigh and many new varicosities in the lower right leg associated with marked edema. A midthigh ligation was done, with retrograde injection of sodium morrhuate. This was immediately followed by marked leg edema and pain. The status of the deep circulation then came up for discussion, since swelling and leg pain followed so promptly after superficial venous obliteration. An attempt was made to obtain a venogram by the incision technic of Bauer, but all the vessels were scarred, and no bleeding was obtained. A superficial lateral ankle vein was then injected by direct venopuncture and an excellent venogram obtained. This showed a perfectly normal intact deep venous system.

COMMENT: This patient had massive lymphedema. In this case, contrary to Case 2, we advised continuation of iontophoresis and supportive Ace bandage, with moderate relief.

Case 5.—H. L., a 52-year-old man with a complaint of left leg pain on arising and heavy feeling in the leg. History of a deep penetrating injury of lower right thigh followed by swelling for some time. Recent Bell's palsy. *Examination* reveals chronic edema of both legs, with desquamating pigmentation and varicose veins of the left calf. Normal arterial pulsations. Ace bandages were advised for the varicose veins. The patient could not wear these because of increased calf pain. This suggested the possibility of deep venous occlusion. A venogram showed a normal deep venous system and moderate arteriosclerosis.

COMMENT: Apparently, our varicose vein picture plus arteriosclerosis was justified. Pain after the Ace bandage was not due to deep venous block but probably to ischemia on the arterial side. Obliteration of the superficial varicosities was justified. In a case of this kind, complicated by several factors, it certainly would be injudicious to obliterate the varices without absolute knowledge of the status of the deep venous system.

Case 6.—G. H., a 67-year-old man complained of rheumatism of the right hip. History of a gunshot wound of the right antecubital fossa, with operative repair 25 years ago. He now has a local tumor, dizziness and tinnitus. *Examination* reveals an arteriovenous aneurysm over anterior portion of right antecubital fossa with moderate enlargement of the arm. B. P. 174/0 right arm; 174/104 left arm. Moderate cardiac hypertrophy. An arteriogram was taken by direct injection of 20 cc. of diodrast into the brachial artery proximal to the aneurysm. This showed multiple arteriovenous communications over an area, four by six centimeters in length, in the antecubital space.

COMMENT: This case showed hypertension and cardiac hypertrophy following an arteriovenous aneurysm. Resection was decided against because of the age of the patient. With the arteriogram it is possible to visualize

the extent, number and location of the arteriovenous communications in case operative procedure is feasible.

Case 7.—M. L., a 44-year-old white male, with recurrent migrating phlebitis for more than 12 years. The patient had had a saphenous vein ligation. For two or three months there was persistent pain and coldness of the right foot and marked intermittent claudication. *Examination* reveals a cold, blue right foot, with painful toes. Absent dorsalis pedis and posterior tibial pulsations. Dilatation of the calf veins and positive tap test in the thigh. Negative Perthes'. A diagnosis of Buerger's disease and varicose veins was made. The deep system was thought to be intact. A venogram was done

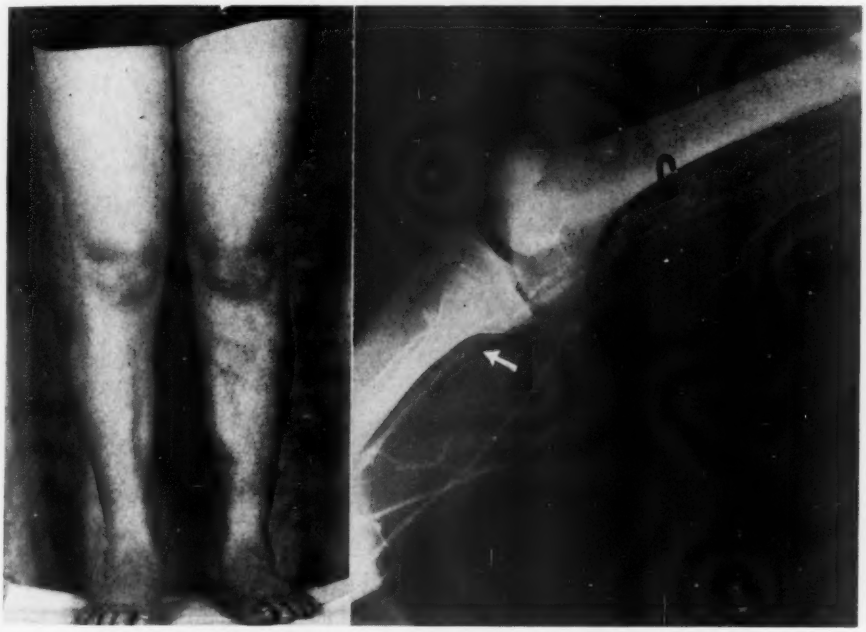


FIG. 3.—Venogram of a case with left calf hypertrophy. (A) Deep venous system. (B) Bulbous dilatation of vein. (C) Multiple intercommunications with bulbous venous dilatation

to visualize the venous changes in Buerger's disease. This showed widely dilated posterior tibial and deep femoral veins with marked irregularity of intima. There were filling defects of the lumen where thrombi were adherent.

COMMENT: This is the only picture we have seen of the marked changes taking place in the deep venous tree in a patient with obvious Buerger's disease (Fig. 4).

Case 8.—P. C., a 55-year-old female, with extensive varicose veins for many years, most extensive in the right leg. There was a prominent right long internal saphenous vein. These were not controlled by a tourniquet at the saphenofemoral juncture and a tourniquet applied to large veins above and below the knee.

COMMENT: A venogram demonstrated four communicating branches from the superficial varicosities of the calf to the deep system. Clinically, these are incompetent. Therefore, the only cure for this patient is a flap

operation to secure each perforator. A high vein ligation and a division of one low branch would result in failure (Fig. 5).

Case 9.—K. C., a 58-year-old white man, developed a postoperative phlebitis following prostatectomy eight months ago. The patient remained in bed for six weeks, with marked swelling of the leg. He could walk for only five minutes before treatment. He was improved greatly with Ace bandage and iontophoresis.

FIG. 4.—Venogram of a patient with Buerger's disease. (A) Femoral vein with multiple filling defects, the site of thrombi. (B) "Splintering" of intima in posterior tibial vein with thrombi.

COMMENT: A venogram showed many collateral superficial vessels and absence of the deep venous system of the calf. This picture is characteristic of the great majority of postoperative phlebites in the location of the venous obstruction. (Fig. 6 and Discussion).

We have studied a number of additional cases by venography in which there was real doubt as to the nature of the deep venous system. In these

cases venography demonstrated that the deep venous channels were intact and it was possible to proceed with definitive therapy to cure the symptoms and disability caused by the varicosities present.

Discussion.—The common postoperative and postpartum disorders of venous thrombosis were thought to be due to deep femoral or peripelvic thromboses. Homans,[5] in 1937, pointed out that the popliteal region and upper calf were probably frequent sites of thrombophlebitis. Roessle,[6] in 1937, found deep calf vein thromboses in 88 of 324 autopsy cases where

Fig. 5.—Extensive varicose veins with multiple incompetent communicators clinically. (A-B-C-D) All point to perforating branches between superficial and deep venous systems.

thorough dissections were done. Thirty-eight had, in addition, thromboses in the femoral vein. Ten had massive pulmonary emboli arising from the femoral vein; but, in addition, there was thrombosis of the calf vein in these cases. Neuman,[7] 1938, has similar figures from postmortem material. Calf thrombosis occurred in 73 per cent and calf thrombosis with femoral thrombosis in 16 per cent. Most conspicuously, however, *there is no case of femoral vein thrombosis with unaffected calves.* Frykholm,[8] in 1939, with careful dissection of 133 cases of venous thrombosis, found 85 per cent occurring distal to the profunda in the femoral vein and primarily in the branches below the knee. Bauer,[2] in 1940, has confirmed this data in the living subject by venography. He has an excellent study of venograms taken to diagnose early postoperative calf thromboses and older healed processes.

In our clinic, an attempt has been made to clarify many of the obscure cases of chronic leg swelling and leg pain in which the status of the venous and lymphatic circulation cannot readily be determined by the usual clinical tests. It was possible to demonstrate a normal deep venous return in the calf of the great majority of chronic leg swellings with or without pain. Chronic lymphedema was thought to play a dominant rôle in the pathogenesis of this condition. It is possible that chronic sepsis may play an important rôle in these cases. This idea was first suggested by Halsted[9] to explain chronic swelling of the arm following radical mastectomy. The use of chemo-

FIG. 6.—Postoperative deep calf thrombosis. (A) Shows the termination of the popliteal vein. No deep venous system is visualized in the calf.

therapeutic drugs of the sulphonamide series may be helpful to stop the inflammatory process. We are treating some of these cases of chronic leg swelling and pain without venous obstruction with these drugs. The results will be described in a later report.

It is necessary to be absolutely assured of the deep circulation in those cases of leg swelling and pain with marked varicosities where the treatment of choice involves sclerosis of the varicosities and high saphenous vein ligation. Case 2 is such an instance, where obliteration of the compensatory varicosities would remove the only remaining venous return in the leg.

It is also possible by the use of this technic to study those not infrequent cases of unilateral calf hypertrophy for circulatory disturbances, as in Case 3.

In arteriovenous aneurysms, where surgery is contemplated, it is of more than academic interest to visualize the extent and situation of the arteriovenous anastomoses, a visualization which is not always simple or safe at the time of operation. It is possible to determine the number of communications, since in some cases multiple openings are present.

CONCLUSIONS

(1) A simplified technic for venography is described.

(2) Its utilization in a number of perplexing cases of leg swelling and pain, with or without varicosities, has been described.

(3) An interesting roentgenogram of the deep venous tree in Buerger's disease is shown.

Appreciation is extended to Dr. S. Rosenzweig, Dr. A. Bloom, and the other members of the Cardiovascular Clinic of the North End Clinic for their helpful cooperation.

REFERENCES

1 Dos Santos, J. C.: Jour. Internat. de Chir., **3**, 625, 1938.
2 Bauer, G.: Venographic Studies of Thromboembolic Disease. Acta Skand. Chir., Suppl., **61**, 1940.
3 Fine, J., and Sears, J.: ANNALS OF SURGERY, **114**, 801, 1941.
4 Dougherty, J., and Homans, J.: Venography: A Clinical Study. Surg., Gynec., and Obst., **71**, 607, 1940.
5 Homans, J.: Venous Thrombosis in Lower Limbs. Am. Jour. Surg., **38**, 316, 1937.
6 Roessle, R.: On the Significance and Origin of Venous Thrombosis of the Lower Legs. Arch. f. path. Anat., **300**, 180, 1937.
7 Neuman, R.: Centers of Origin and Forms of Development of Thrombosis of the Leg. Arch. f. path. Anat., **301**, 708, 1938.
8 Frykholm, A.: Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis. Surg., Gynec., and Obst., **71**, 307, 1940.
9 Halsted, W. S.: Surgical Papers, Johns Hopkins Press, Balt., 1924.

A SUBCLAVIAN ANEURYSM CURED BY CELLOPHANE FIBROSIS

PAUL W. HARRISON, M.D., AND JACOB CHANDY, M.B., B.S.

BAHRAIN, ARABIA

THREE YEARS AGO, Pearse[1] reported to the American Surgical Association that he had been successful in producing a gradual occlusion of the aorta in dogs. Wrapping the vessel with ordinary DuPont cellophane had led to a fibrosis which had eventually closed it off by its contraction. The ability of cellophane to produce this type of tissue reaction was used by Page[2] in the production of perinephritis with persistent hypertension. We ourselves have had occasion to study this fibrosis in experimental work on herniae.

Since the above report was made, we have had the opportunity to try out the method in two human cases. One of these attempts was successful, as indicated by the title of this paper, while the other eventuated in ligation of the involved artery with an unsatisfactory result.

Case 1.—On July 7, 1941, Hussein bin Mohammed, a weather-beaten, old pearl diver, age 70, or more, reported to the Mason Memorial Hospital complaining of very severe pain in his left shoulder. It was not entirely clear just when this pain started but apparently it had excited his attention for less than six months. Its intensity had greatly increased during the few preceding weeks.

Physical Examination.—The patient was a thin, hardy old man, in good general condition. The pain which was distressing him arose from a pulsating mass the size of a hickory nut, which appeared to be connected with the third portion of the left subclavian artery. There was a loud bruit and usually a palpable thrill. The pain radiated up into the neck and to some degree to the shoulder and upper arm. The mass itself was not tender. The systolic blood pressure in the left arm varied, but a reading of 130/70 was usually obtained. Roentgenologic examination of the shoulder area was negative. The Kahn test was negative. *Clinical Diagnosis:* Aneurysm of the third portion of the subclavian artery. Although it was realized that ligation of the subclavian can usually be carried out without gangrene of the extremity, it was decided to try the effect of cellophane fibrosis on this case.

Operation.—July 8, 1941: Under local anesthesia, with one per cent novocain solution with adrenalin, the mass was exposed by a three-inch incision below the clavicle. The intervening muscles were cut in the line of the incision. Adequate exposure was easily obtained. The aneurysm presented itself as a fusiform swelling in the course of the artery, about 2.5 cm. in length and 1.5 cm. in diameter. Two small arteries coming off the dilated portion were doubly ligated and cut. The aneurysm was careully exposed and slightly more than one centimeter of normal artery both proximally and distally (Fig. 1).

Cellophane tape, one centimeter in width, was boiled and ready for use. We found that boiling is not the best way to sterilize the tape, because it was rendered so bodiless and fragile that it was almost impossible to lay it in place accurately. A five-layer band was applied proximally, and fastened with a single suture on the anterior surface. A less satisfactory application was made distally, after which the muscles were brought together as accurately as possible, and the skin was sutured.

The operative wound healed without incident. He developed an attack of malaria

in the hospital which was treated with quinine. His pain was unrelieved by operation. He had been told in advance that this would be the case, but he was much disappointed. He was discharged on the seventeenth postoperative day, after he had promised to return for inspection every month.

Subsequent Course.—In spite of his promise, the patient did not return for follow-up visits. In May of the next year, we posted a reward of five rupees for his discovery, and found him living only five miles away. He was now delighted with the result of the operation, for the pain was almost gone and he was planning to return to his work as a pearl diver. For our part, we were much disappointed, for the aneurysm was no smaller. Indeed, it seemed definitely larger, although this may have been due to atrophy of the overlying muscles which brought it closer to the examining finger. Moreover, its pulsatile thrust seemed as strong as ever. Between the aneurysm and the entering artery was a sharp groove which, at this point, reduced the diameter of the artery by at least one-half. This groove was astonishingly narrow, and we wondered if it would have been better to use a wider tape (Fig. 1 C).

The patient's general condition was good. He had improved somewhat with the disappearance of the pain. We hoped, but by no means felt sure, that there would be no further enlargement of the aneurysm. In any case, the fibrosis has progressed encouragingly. It seemed that with a little further contraction, the aneurysm must begin to shrink in size.

On October 28, 1942, five months later, the patient was observed again. He had not returned to his pearl diving because of age and general pains, but apparently it was not the aneurysm that kept him home. We were delighted to find that the aneurysm had shrunk until its diameter was about the same as that of the artery. The examining finger following the subclavian artery now felt only two sharp grooves, separated by one and one-half centimeters. It was interesting to note that the pulsatile thrust of this small remnant of the aneurysm was not notably less than that of the artery proximal to it. The systolic blood pressure was more stable now. It was maintained on the left side at a level about ten points higher than that on the right (left, 130/70; right, 120/80.

On February 8, 1943, the patient was looked up again. It was expected that the aneurysmal sac would be completely obliterated by this time, and this hope was not disappointed. The subclavian artery was interrupted by a deep groove, filled with a fibrous mass (Fig. 1 E). The size of the mass was difficult to determine; it was perhaps slightly more than half a centimeter in length. The pulse on the left side was perceptibly delayed as compared with the right. The blood pressure on the left was 136/96; on the right 120/72. There was no pain in the shoulder area, and cure appeared to be complete.

Case 2.—Jebber Musellim, a pearl broker, age about 70, came to the Mason Memorial Hospital, March 22, 1942, complaining of severe pain in the left shoulder. The history was very similar to that of the first case. The pain had increased so much during the preceding 48 hours that he was rather desperate and insisted that something be done at once.

Physical Examination.—The patient, a tall, thin man, in good general condition, except for the presence of bronchitis. Below the lateral portion of the left clavicle was a pulsatile mass, apparently a little smaller than that in Case 1. There was a loud bruit and palpable thrill.

The patient's pain was so severe that we urged him to come in at once for treatment. We explained that we greatly feared rupture and would suggest immediate operation. The patient refused this, and decided to try Arab medicine, and, sick as he was, he went home, where the region of his pain was branded with a red hot iron in a number of places. One vertical brand, half an inch wide and nearly two inches long,

was placed exactly over the pulsating swelling. These brands relieved the pain a little and he remained away from us for 48 hours. At the end of this time, he appeared and begged for the operation. He had been given sulfapyridine tablets to use at home, and his bronchitis was better. However, his temperature ranged from 100° to 101° F. The systolic blood pressure in both arms was 136. The Kahn reaction was negative.

Operation.—March 24, 1942: The exposure of the aneurysm was similar to that of Case 1. However, the skin incision was complicated by the presence of the branded areas. These areas had been cleaned with great care, and touched with carbolic acid. The incision missed all of them except the vertical brand over the swelling itself. In spite of these procedures, wound infection, which almost cost the patient his life, ensued. The futility of trying to sterilize the necrotic skin was obvious.

The aneurysm was found to be about 1.5 cm. in diameter. Distally, two branches of equal size left the swelling. Cellophane tape was wrapped about the artery proximal to the enlargement, and around each of the large distal branches. This time, the cellophane had been sterilized by a two-day immersion in alcohol instead of boiling, and it was easily handled.

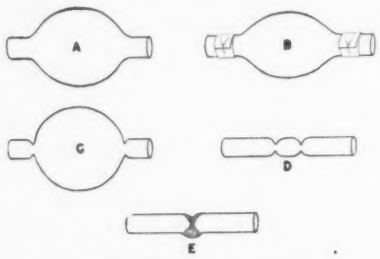


FIG. 1.—Diagrammatic representation of changes in aneurysm in Case 1. A. Preoperative impression. B. Immediately postoperative, cellophane applied. C. Condition at time of first follow-up examination, May, 1942. D. Marked shrinkage of aneurysm noted Oct. 28, 1942. E. Last observation Feb. 8, 1943.

On the fourth postoperative day it was realized that infection had set in. On the sixth day the incision was reopened, with the escape of an ounce of pus. The infection seemed to be clearing up until, at midnight on the eleventh day, there was a profuse hemorrhage from the wound. The patient was found in a pool of blood, the bleeding having stopped for the moment. He was taken to the operating room and the wound was explored. There was found a tear of one of the ligated distal branches. The opening was plugged by a friable clot, which came away when touched, causing alarming hemorrhage again. This was checked by lifting the artery by means of its cellophane collar and temporarily occluding the lumen. It was out of the question to deal with this situation by means of cellophane tapes, so a triple ligation was carried out. The wound was then closed about a small drain.

The patient was given saline and glucose infusions. His left arm was kept encased in cotton wool. For the first 24 hours the arm was cold, and the patient complained of great pain. Following this, it gradually became warmer, and within a week the pain had practically disappeared. There was no definite paralysis but rather a general weakness of all muscle groups. The patient remained in the hospital 31 days. His wound healed firmly. There was no further hemorrhage. The weakness of the left arm did not improve and wasting of the arm became increasingly evident. At the time of his discharge, the circumference of the left arm at the midbiceps level

was three centimeters less than the right. There was marked interosseous atrophy. Small objects, such as a pen, could not be picked up.

About four months after the operation, a Pavaex machine was secured, and a half-hour of treatment was applied every other day for three months. There was slight improvement, so that he can now handle small objects better. It is probable that the arm will be permanently crippled.

SUMMARY

1. An aneurysm of the distal portion of the subclavian artery has been cured by means of the fibrosis induced by cellophane tape wrapped around the vessel.

2. It took ten months for the arterial occlusion to progress sufficiently to cause the aneurysm to diminish in size, and 19 months for the process to be completed.

3. A comparable case was treated by ligation, with the result that there is considerable disability in the arm.

4. We believe that this method of gradual arterial occlusion is valuable, and that it might be applied to aneurysms of other arteries, notably the aorta.

REFERENCES

[1] Pearse, H. E.: Experimental Studies on the Gradual Occlusion of Large Ateries. Trans. Am. Surg. Assn., **58**, 443–457, 1940; *idem:* ANNALS OF SURGERY, **112**, No. 5, 923–937, November, 1940.

[2] Page, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis. J. A. M. A., **113**, 2046, 1939.

THE COAGULABILITY OF VENOUS BLOOD OF NORMAL AND DISEASED LEGS*

A STUDY ON 191 SUBJECTS

B. G. P. SHAFIROFF†, M.D.,
BROOKLYN, N. Y.

H. DOUBILET‡, M.D., I. S. BARCHAM, M.D., and CO TUI, M.D.,
NEW YORK, N. Y.

FROM THE LABORATORY OF EXPERIMENTAL SURGERY, DEPARTMENT OF SURGERY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK, N. Y.

THERE has been in recent years a gradually increasing interest in the differences between the blood of diseased and that of normal extremities. Thus, blood drawn from varicose veins associated with complications has been found, on the basis of comparison with values accepted as normal, to exhibit an increase in viscosity and in the concentration of plasma proteins;[1] in carbon dioxide combining power;[2] and in the rate of sedimentation.[3]

The clotting time, also, has been studied; and while in the venous blood of thrombo-angiitis obliterans, it was found by Theis[4] to be shortened in some cases even to less than one minute, in the blood drawn from varicose veins, it was found to be "within normal limits." However, the normal values for viscosity, concentration of plasma proteins, of the carbon dioxide combining power, and of the rate of sedimentation, do not vary within the wide range that the clotting time does, so that a clotting time could vary 300 per cent and still remain "within normal limits." In order, therefore, to determine if there are any actual changes in the clotting time of the local venous blood of an extremity, it would be more reliable to use not the figures accepted as within normal limits, but the clotting time of the blood drawn at the same time from the normal extremity of the same individual. In the following study, this criterion was observed, the venous blood of a normal upper extremity serving as a control.

METHOD.—One hundred ninety-one subjects, comprising four principal groups, were studied. Group I consisted of 28 normal students who had no detectable peripheral vascular disease. The results from this group serve as control for the evaluation of results obtained in the subsequent groups. Group II consisted of 115 patients with varicosities of the lower extremities which were being treated by injections of sodium morrhuate. In this group were many advanced cases, with such complications as varicose ulcers, dermatitis, or peripheral edema of the affected extremity. Determinations of the coagulation time of the blood in the latter individuals, who had been treated with sodium morrhuate, were made only after one to three weeks had passed since the last treatment. In Group III there were 36

* Aided by a grant from the New York Foundation.

† B. G. Shafiroff, M.D., at present Major, M.C., United States Army.

‡ H. Doubilet, M.D., at present Captain, M.C., United States Army.

subjects suffering from conditions comparable to those in Group II, excepting that these patients had never received any treatment. Group IV comprised seven cases of postoperative venous thrombosis and five cases of primary acute thrombophlebitis.

The coagulation time of the blood from the upper and lower extremity was determined in each individual. Blood from the upper extremity was obtained from a cubital vein, that from the lower extremity from the internal saphenous vein at the ankle when there was no varicosity, as in Groups I and IV. In cases in whom there were varicose veins, as in Groups II and III, the blood was drawn from a varicose vein which had not been previously injected.

The determination of the clotting time was carried out according to the technic of Lee and White.[5] The vein was pierced by a fine hypodermic needle after the application of a tourniquet, and one cubic centimeter of blood was drawn rapidly into a dry syringe. One-half cubic centimeter of blood was placed each in one of two small test tubes and duplicate determinations made simultaneously by two observers. The test tube was tilted at regular intervals until it could be inverted without displacement of the blood mass. This was taken as the critical point for the clotting time. The test was repeated when delay or difficulty was encountered in the process of withdrawing blood from the vein or when any other fault in technic occurred. In 191 subjects, 352 duplicate sets of determinations were made. In none of these was there a difference greater than 20 seconds in the determinations of the two observers, most of the differences being in the nighborhood of ten seconds. The values of the clotting time of the blood from the arm and leg were compared, and the results tabulated in Tables I and II.

TABLE I

ANALYSIS OF INCREASED COAGULABILITY OF BLOOD OF LEG

Group	Total No. of Cases	No. of Cases with Hypercoagulability	Per Cent of Total	Acceleration in Excess of 59 Seconds		Average Acceleration Time	Maximum Acceleration Time
				No. of Cases	Per Cent of Total		
I	28	17	60%	0	0%	30″	59″
II	115	83	72%	39	33%	70″	285″
III	36	28	77%	13	36%	60″	132″
IV	12	11	92%	9	75%	146″	284″

RESULTS.—Referring to Table I, one observes: (1) That there is a slight tendency for venous blood from the lower extremity of normal individuals (Group I) to clot more rapidly than that from the upper extremity; *i.e.*, in 60 per cent of the total number of cases. (2) The blood from varicose veins of individuals in Groups II and III showed an exaggeration of this tendency to faster clotting (72 and 77 per cent, respectively) than the venous blood from the upper extremities of the same individual. (3) In the cases with thrombophlebitis (Group IV) blood from the lower extremity clotted more rapidly than that from the upper extremity in 92 per cent of the cases. (4) Taking those cases of all Groups in which the blood

clotted more rapidly from the lower extremity, the average acceleration in Group I was only 30″, whereas in Groups II and III comprising the varicose veins, the average acceleration was 70″ and 60″, respectively; and in those cases of Group IV with thrombophlebitis the average acceleration was 146″. The greatest acceleration in Group I was in one individual, and that was 59″. In Group II, the maximum acceleration was 285″, while in Group III it was 132″. Thirty-three and 36 per cent of the cases with hypercoagulability of varicose vein blood for the two respective groups showed acceleration times in excess of the 59″, noted above as the maximum for normal individuals. In Group IV, the maximum acceleration time was 284″, while 75 per cent showed acceleration times in excess of 59″.

It was previously stated that there was a difference of about 10 to 20 seconds in the determinations by the two observers on any one blood. This may be considered as inherent in the technic. Making allowances in one case for an experimental error of ten seconds and in another case of 20 seconds, the results may be regrouped as in Table I, which may be analyzed as follows:

TABLE II

ANALYSIS OF COMPARATIVE COAGULABILITIES OF VENOUS BLOOD OF UPPER AND LOWER EXTREMITIES-REGROUPED ON BASIS OF OBSERVATIONAL ERROR

	Group I	Group II	Group III	Group IV
(A) 10-Second Observational Error				
Equal	5 (18%)	18 (16%)	9 (25%)	0 (0%)
Leg > arm	15 (53%)	80 (69%)	24 (64%)	11 (92%)
Arm > leg	8 (30%)	17 (15%)	3 (9%)	1 (8%)
(B) 20-Second Observational Error				
Equal	13 (46%)	35 (30%)	12 (33%)	0 (0%)
Leg > arm	12 (43%)	72 (62%)	23 (64%)	11 (92%)
Arm > leg	3 (11%)	8 (8%)	1 (3%)	1 (8%)

For the normal individuals in Group I in the 10-second range of error, only 53 per cent of the cases showed hypercoagulability of lower extremity blood as compared with the upper extremity blood, while the clotting time of the upper extremity blood was faster in 30 per cent of the cases, the remaining 18 per cent being equal. In the 20-second range of error tabulation, blood from the lower extremity clotted more quickly in only 43 per cent of the cases, while upper and lower extremity blood coagulability was equal in 46 per cent of the cases. In no instance did the blood of the lower limb clot more rapidly than the blood of the upper limb by more than 59″.

In Groups II and III, however, the results were definitely different. In the ten second range of error tabulation, the blood from the varicose vein was hypercoagulable as compared with the venous blood of the upper extremity in 69 per cent of the total cases in Group II, and 64 per cent of the total cases in Group III. The upper extremity blood was more coagulable in only 15 and 9 per cent of the cases for the two respective groups. When the range of error was set at 20″, the same tendency is to be observed. Sixty-two of the cases in Group II, and 64 per cent of those

in Group III, showed a greater clotting tendency of blood from the varicose veins, whereas in only eight and three per cent, respectively, did the venous blood from the upper extremity clot more rapidly. In Group IV, 92 per cent of the total cases showed the blood from the lover extremity to be more coagulable than upper limb blood, whereas the reverse was true in only eight per cent of the cases, these results being the same whether the range of error was as 10″ or 20″.

In those cases where thrombophlebitis had already become established, there was also an associated marked change in the coagulability of the blood of the diseased extremity as compared with that from a normal extremity of a thrombophlebitis individual. This is plainly visible in the tables. In Groups II and III, it is likewise seen that there is a strong tendency for the same to be true, although not with as great a frequency. This is probably due to the great variation of the degree of disease in the affected vein in both these groups, whereas in cases with established thrombophlebitis, the maximum degree of disease of the affected vessel had taken place. In other words, there are a number of cases in both Groups II and III in which the disease of the affected vessel was so mild as not to interfere with the characteristics of the blood therein. These cases detract from the percentage which might be high enough to present significant differences in the characteristics of blood in a vessel with well-established disease.

There is, thus, a distinct tendency towards acceleration of coagulation in the blood of varicose veins. Where such differences occurred, the magnitude was two times greater than the average difference of the normal individuals, and the maximum difference was five times greater than the maximum difference of the normals. In the cases with established thrombophlebitis, this hypercoagulable tendency of blood of the diseased extremity was so marked, that the average acceleration was four and one-half times greater than in normal subjects, and the maximum five times greater.

Comments.—Some speculations evoked by the above findings may be set down in an attempt to relate this work to its possible clinical use. In regard to the subject of varicose veins, the following questions arise: (1) What change takes place in the blood of a diseased extremity which is reflected in the increased tendency of the local blood to clot more readily than that from the normal extremity of the same individual? (2) Does this rapidity of clotting increase with the functional impairment of the physiology of the veins? (3) Does it disappear in the recumbent position? (4) Do varicose veins showing this hypercoagulable tendency predispose to the development of postoperative thrombo-embolization?

In regard to the marked acceleration of clotting of blood from the veins of extremities with established thrombophlebitis another set of questions may be set down: (1) Is this tendency due to the same change as is to be found in varicose vein blood? (2) Does it antedate the formation of the thrombus?

(3) If so, may it not be developed into a prognostic test which would indicate preventive therapy before actual thrombo-embolization takes place? Each of the answers to these seven questions would constitute the definitive result of seven lines of further investigation.

SUMMARY

1. A study of the coagulation time was made of the blood from the upper and lower extremities of 191 subjects—28 normal, 156 with varicose veins, and seven with established thrombophlebitis.

2. There was found in normal persons, a slight tendency of lower extremity blood to clot faster than upper extremity blood.

3. This tendency was moderately exaggerated, in various degrees, by the presence of varicose veins, and markedly exaggerated in the blood from thrombophlebitic extremities.

4. The possible implications of these findings were discussed.

REFERENCES

1 Heller, R. E.: Pathological Physiology of Varicose Veins. Surg., Gynec. and Obst., **71**, 566, 1940.

2 DeTakats, G., Quint, H., Tilletsin, B. I., and Crittenden, P. J.: Impairment of Circulation in the Varicose Extremity. Arch. Surg., **18**, 671, 1929.

3 Erb, K. H., and Tiefensee, K.: Untersuchungen über das Krampfaderblut. Beit z. Klin. Chir., **152**, 400, 1931.

4 Theis, F. V., and Freeland, M. R.: The Blood in Thrombo-angiitis Obliterans. Arch. Surg., **38**, 191, 1939.

5 Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of the Blood. Am. J. Med. Sci., **145**, 495, 1913.

BOOK REVIEWS

THE HEMORRHAGIC DISEASES AND THE PHYSIOLOGY OF HEMOSTASIS. By A. J. Quick, M.D. Charles C. Thomas, 340 pp., $5.00, Springfield, Ill., 1942.

This work, which is an expansion of the Beaumont Lectures given by the author in 1941, represents the first methodical and comprehensive effort to analyse the Hemorrhagic Diseases from the pathophysiologic standpoint. The author wisely stresses the fact that the work is not a treatise on blood coagulation. It intends to deal with this topic as one of the factors sharing in the mechanism of hemostasis. Alterations of this mechanism are regarded as the fundamental causes to be sought in the study of the Hemorrhagic Diseases.

Contradictory departures from his avowed purpose are, however, evident here and there. At the outset, a chapter deals not with the history of hemorrhagic disease or of hemostasis in general, but with the "History of the Coagulation Mechanism." Hemostatic factors other than those related to blood coagulation, e.g., vascular and extravascular factors, receive scant attention For example, purpuras of the Henoch and Schoenlein type, which might well result from alterations in those factors, are dismissed with the remark (p. 132) that "only the thrombocytopenic purpuras are primarily hemorrhagic diseases." Due prominence is given to the rôle played by the blood platelets in hemostasis. There is a good discussion of thrombopenia, its manifestations, course and treatment. Hereditary thrombasthenia (Glanzmann), the only authentic disorder of hemostasis due to a qualitative defect in the blood platelets, receives passing mention only. The reader is given the impression that this disorder should actually be grouped with the "pseudo-hemophilia" of von Willebrand, the cause of which resides probably in the vessels. Much confusion, however, exists even in the current medical literature, concerning these two diseases.

The author is at his best in the chapters dealing with blood coagulation. There he examines and reports fully, and, on the whole, impartially, the mass of evidence accumulated on this controversial subject during the past 50 years. The discussion is enlivened by the author's personal comment made pointed by intimate knowledge of a field in which he played such a leading part.

An appendix dealing with technical methods supplies directions for the performance of many tests, important information, unobtainable elsewhere, under one cover. The book should prove of great value to other workers in the field of hemostasis and its disorders. Throughout the text the reader may pick up stimulating leads, valid (even when tart) criticisms on method and interpretation and much imaginative spanning of seemingly unrelated facts. This reviewer knows of no similar work on the subject to date, in which the facts are so clearly exposed, the evidence so well grouped and shrewdly examined and its possible implications so brilliantly outlined.

LEANDRO M. TOCANTINS, M.D.

ABDOMINAL AND GENITO-URINARY INJURIES, MILITARY SURGICAL MANUALS III, NATIONAL RESEARCH COUNCIL. W. B. Saunders Co., 243 pp., $3.00, Philadelphia and London, 1942.

The soundness of the views expressed in this volume is attested by the membership of the Committee on Surgery of the Division of Medical Sciences of the National Research Council and its subcommtitee on Urology, as well as by the experience and knowledge of Dr. Ambrose H. Storck, who prepared the section on Abdominal In-

juries, and of Dr. Clark M. Johnson and Dr. H. M. Weyrauch, who contributed to the section on Genito-Urinary Injuries.

It is so thoroughly sound and fair that it may not always help the isolated medical officer to a definite decision on the procedure he should follow.

Certain procedures are definitely condemned and perhaps the book is most valuable for these warnings.

WALTER ESTELL LEE, M.D.

FIRST AID, SURGICAL AND MEDICAL. By Warren H. Cole, M.D., and Charles B. Puestow, M.D., M.S., Ph.D. Appleton-Century Co., New York. 1942.

The authors have compiled, with the assistance of a formidable list of contributing authors, a modern version of emergency treatment.

The book is well arranged, beginning with the limitations and precautions of first aid work; proceeding with an intelligent outline of anatomy and physiology as a basis for the reader to appreciate the reasoning upon which subsequent chapters are based. The illustrations are good and the individual chapters on specific subjects are well arranged. The early use of the sulfa drugs is stressed, and there is an agreeable absence of antiseptic measures often noted in other texts on this subject.

An excellent chapter on transportation of the injured is included.

The problems of respiratory emergencies are treated as a group so that the student is prepared for the treatment of such emergencies occuring from either respiratory arrest or respiratory obstruction.

Medical emergencies in contradistinction to surgical emergencies are discussed, giving the reader an intelligent approach in caring for such conditions.

The book may safely be recommended as a guide for medical students as well as an advanced text for those who have had previous first aid training.

WILLIAM V. HEALEY, M.D.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.